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Editorial

The Risk of Coronary Heart Disease

A RECENT EDITORIAL in this journal[1] attempted to stimulate consideration of the significance of follow-up studies pointed to coronary or arteriosclerotic heart disease (ASHD). Unfortunately, we took too much for granted. It appears that these findings are far from being as well known as we had thought.

On the firing line of research on ASHD, where everyone is busy attacking the unknown (and occasionally pot-shooting his colleagues), the battle goes on about mechanisms in pathogenesis, the details of lipid metabolism, the degree of association among variables, and what may be inferred about final causes in the "coronary problem." The argument is especially loud when the question is raised as to how far present knowledge should be applied in efforts at preventive programs. From a little way off all this heat may appear only as smoke; what is really known may be missed in the confusion. It seems worthwhile, therefore, to point out some findings from research on populations, avoiding controversy, we hope, by concentrating on what is actually observed and foregoing the pleasure of attempting mechanistic explanations.

Studies on Populations

Epidemiologic studies seldom provide final answers to questions about mechanisms and ultimate causes but they are producing facts that cannot be ignored if the problem of coronary heart disease is to be seen in proper perspective. We may debate as to *why* some people are more susceptible than others but epidemiologically we *can* distinguish people who differ in their risk of coronary heart disease. Everyone knows that women have less risk than men and that the risk rises steeply with age in both sexes. More to the point is what is found among persons of the same age and sex.

It is indisputable that the risk of ASHD among middle-aged men is by no means the same in various populations or even in the same population at different times.[2-4] No one will deny that something in the mode of life is involved. For example, the frequency of coronary heart disease among men in Japan or southern Italy is far less than that of men of the same age in the United States, but within the United States it does not appear that men of pure Japanese or Italian ancestry are remarkable in respect to the risk of coronary heart disease. ASHD is the leading cause of death among Japanese Nisei in California, and the frequency of the disease among Japanese in Hawaii is intermediate between California and Japan.[5,6] In Boston the representation in hospitals of ASHD among men of Italian ancestry is much the same as among other Americans and far greater than observed among Italians in Italy.[3,7]

There is no lack of other examples indicating that the way people live must have a profound influence on their susceptibility to this disease. While controversy continues as

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to what aspects of the mode of life are most influential, it is profitable to consider, in groups differing as to risk of ASHD, measurable characteristics that conceivably have relevance to the development of this disease. Besides cross-population comparisons, follow-up studies are of particular interest.

Characteristics Associated with Increased Risk

The experience of life insurance companies long ago showed that the risk of death from heart disease is increased in persons with high blood pressure and who are unusually heavy for their height and age. These relationships are emphasized further in the most recent large-scale actuarial analysis.[8] But the findings from several other recent follow-up studies go much further, both in regard to the variables studied and in the security of identification of ASHD as the major threat. A little over a decade ago research programs began in which groups of men were examined and their subsequent health was followed in the attempt to discover what characteristics observed in health have prognostic significance for future ASHD. These investigations, and others begun later, are still in progress; some results have been reported and others are coming in.

Among middle-aged men in this country the annual incidence of new ASHD is of the order of 1 per cent. Accordingly, though the number of men under observation in follow-up studies is relatively small—only a few thousand in all—significant results are available after only a few years. The findings from these researches in different parts of the country are so consistent that the relationships observed must have general significance.

The U.S. Public Health Service is conducting a long-time study on a cross section of the adult population at Framingham, Massachusetts. Besides examinations designed to reveal clinical diseases, data were recorded on many personal characteristics. After 4 years of follow-up, new ASHD was recorded in 52 cases among 898 men aged 45 to 62 and clinically well at the first examination.[9] Among many pre-disease variables considered, three were outstanding in regard to the development of ASHD in the 4-year follow-up. These were the arterial blood pressure, the relative body weight, and the concentration of cholesterol in the blood.

Among the few men with definite hypertensive heart disease on first examination, the rate of subsequent development of ASHD was over three times that experienced among the normotensive men (B. P. less than 140/90), and the rate was intermediate among the men who had elevated blood pressure without hypertensive heart disease when first seen. Relative body weight, too, was significant at Framingham. Among the 20 per cent of the men with the highest relative weights the rate of new ASHD was more than twice that among the other men. Finally, the 20 per cent of the men with the highest serum cholesterol values subsequently developed ASHD at three times the rate of the other men.

Further analysis to eliminate the effect of intercorrelation among these measured variables indicated that the prognostic significance for ASHD of both blood pressure and serum cholesterol is much higher than the relative body weight. At the 6-year follow-up consideration of other variables yielded less significant relationships to new ASHD.[10] Neither national origin nor alcohol consumption showed any significance. There was an inverse correlation between the incidence of ASHD and educational status; men with grade-school or less education had a rate of 14 per cent above that expected while college men had a rate only 74 per cent of expectation. Cigarette smoking was associated with an increased incidence of ASHD and also with higher serum cholesterol levels, though not with blood pressure or relative weight.

Continued follow-up of the Framingham population, now covering 8 years, has enlarged the "yield" of ASHD with no essential change of the picture indicated above, but the relationships have become more and more significant statistically.[11] In Framingham, at least, blood pressure and serum cholesterol certainly have much actuarial importance;

relative weight as an independent variable seems to contribute considerably less to prediction.

In 1949 a follow-up study was started on civil service employees in Los Angeles. A preliminary report of 50 cases of new ASHD in a 2- to 3-year follow-up[12] has been followed by an analysis of 117 new cases developing in 8 years among 1,503 white men. Again serum cholesterol, blood pressure, and relative weight proved to be of outstanding interest.[13]

In the Los Angeles men the age-adjusted rate of new ASHD among the 22 per cent of the men with highest relative weight was 25 per cent above that of the other men. Definite hypertension was found at the original examination in 11.7 per cent of the men in the sample; this was much more significantly prognostic than weight, being associated with subsequent rate of new ASHD nearly twice that of the other men. There was no evidence that "borderline hypertension" was important. Finally, the serum cholesterol concentration proved to have high significance, the age-adjusted rate of new ASHD decreasing steadily from 12.6 for the 102 men with the highest cholesterol values to 5.6 for the 139 men in the lowest cholesterol category. Interesting results were obtained by intercorrelation analysis which, again, emphasized the importance of serum cholesterol in prognosis. For example, when only the hypertensive men were considered, the age-adjusted rate of new ASHD increased as the serum cholesterol level increased.

In 1953 the New York State Department of Health began a study at Albany, similar to those at Framingham and Los Angeles, on male civil service employees aged 39 through 55.[14, 15] After 44 months ASHD had developed in 57 men among a population of 1,843 at risk. Six cases occurred among the 77 men comprising the top 4 per cent in relative body weight, whereas only two or three would be expected on the null hypothesis, but for the material as a whole no statistical significance regarding the risk of ASHD could be attached to relative body weight. Similarly, the occurrence of six cases of ASHD among the 113 men with diastolic blood pressure of 110 or more seems a little excessive (about four would be closer to expectation) but no statistical significance could be attached to the blood pressure in regard to ASHD risk.

But at Albany, as in the other studies, the risk of ASHD was related to the level of cholesterol in the blood at the first examination. The rate of new ASHD among the 209 men in the top eighth of the distribution of cholesterol values in the study population was 77 per 1,000 compared with slightly under 23 for the other men.

One other major follow-up study focused on prediction from blood measurements of the risk of ASHD provides significant data. The "Cooperative Study" involved follow-up for 2 to 3 years of 3,462 men in various parts of the United States whose serum cholesterol values were measured and who were not found to have evidence of ASHD on the initial examination when they were aged 40 to 59.[16] Among these men definite myocardial infarction or coronary thrombosis by clinical plus laboratory evidence occurred in 37 men, 32 of whom were found to have been above and only five below the serum cholesterol median at the time of the initial examination. In other words, the risk of this development of ASHD was six times greater among the above-median men than among the men in the lower half of the cholesterol distribution.

In the winter of 1946-1947 we began a long-time program involving the annual examination of 286 middle-aged business and professional men in Minneapolis and St. Paul. Almost all the survivors among these men have been examined every year, and the follow-up in general has been essentially complete. But we set our sights too low in regard to numbers and, fortunately for the group but unhappily for the statistical analysis, the incidence of new ASHD in this group has been below expectation. However, the findings are of interest because of the relative homogeneity of the sample in regard to age (45 to 55 at the start), occupation and social status, the closeness of the follow-up for so long a time, and the security of the

diagnoses. During 13 years, 16 of these men have died from coronary heart disease, 12 others survive after one or more myocardial infarctions, and one man has developed typical angina pectoris plus electrocardiographic changes of the left ventricular ischemia pattern.

A detailed analysis of the Minnesota data, including the complications of variations and trends in blood pressure and serum cholesterol over the years, will be presented elsewhere.[17] Among the 29 men who developed definite ASHD, 22 were consistently above the sample median in regard to serum cholesterol concentration before the appearance of clinical disease and two others developed high values (285 mg. per 100 ml. or more) before infarction. On the other hand, neither relative body weight nor blood pressure had much prognostic significance in this series. Men with hypertensive heart disease were not accepted in the original sample but blood pressure per se was not a reason for exclusion. Among the 286 men of the sample at the first examination, 46 had relative body weight of 15 per cent or more above the average and 24 men had diastolic blood pressures of 90 mm. or greater. Among the 29 men who later developed ASHD, eight had a relative body weight as great as 115 per cent and only three had a diastolic blood pressure as high as 90 mm. when first seen. It is of interest, however, that eight men, initially normotensive, who subsequently developed ASHD, showed hypertension in later years before infarction or death from coronary heart disease.

Importance of Serum Cholesterol

The results from all the follow-up studies consistently emphasize the importance of the concentration of cholesterol in the blood serum. Roughly, it appears that when any group of middle aged American men is subdivided into upper and lower halves in regard to serum cholesterol level from a single measurement, the men in the upper category prove to have, during the next few years, about three times more risk of ASHD than the men in the lower category. This fact is in general agreement with the findings in population comparisons.

Without exception, so far, samples of men in populations known to have a high incidence of ASHD prove to have higher average serum cholesterol concentrations than men of the same age in populations that suffer a relatively low incidence of the disease.[2-4, 6, 7] Even in comparisons between areas of the same country or between subgroups of the same populations, this principle holds. For example, ASHD is exceedingly common in Finland but the disease is more frequent in the eastern than in the western part of the country, and the serum cholesterol levels correspond.[18] Comparison between Slavonia and Dalmatia in Yugoslavia shows a similar parallelism.[19]

Such examples of the relationship of the serum cholesterol level to the risk of ASHD can be cited almost indefinitely—various types of Jews in Israel,[20] population subgroups in Guatemala,[21] and so on. The London busmen are of particular interest because of the finding that the drivers have a greater risk of ASHD than the conductors. This question as to why? is still unresolved but it is clear that the drivers, compared with conductors of the same age, are more often fat, more frequently have elevated blood pressures, and they have higher serum cholesterol values.[22]

It may be that there are other parameters, particularly other measures of lipids in the blood, that will be found to be as significant as the serum cholesterol in regard to risk of future ASHD. So far at least, none has been proved to be better, and the amount of evidence on cholesterol is far greater than adduced for any other measure. Blood pressure seems to discriminate less well, particularly if we eliminate persons who already show signs of clinical hypertensive heart disease. And there appears to be no doubt that the cholesterol measurement is far more significant than the relative body weight. A cholesterol measurement is certainly not an infallible guide as to the future of the individual, but it is remarkable that in the strict actuarial sense a single measurement easily

classifies men into categories with a three-fold difference in risk.

The finding that serum cholesterol measurements tend to differentiate victims of coronary heart disease from their clinically healthy controls *before* the appearance of the clinical disease destroys the argument long used to invalidate comparisons between patients and their healthy counterparts. The tendency toward relative hypercholesteremia observed in patients is not a result of the disease itself. This gives special significance to the fact that, wherever they are studied, patients with coronary disease predominantly represent the upper part of the distribution of serum cholesterol values in the population from which the patients are drawn—businessmen in Minnesota, bankers in Naples, poor clerks or manual laborers in southern Italy.[26]

But this is not all. The significance of the blood cholesterol level for future risk is underestimated in the follow-up data mentioned above. This is clear when we think about the way in which the data were obtained and analyzed. The principle involved is important and has general applicability; so a diversion here to consider variability and error is warranted.

Variability and Error

Suppose men are classified into two categories in respect to any given variable and then the subsequent appearance of ASHD (or any other new development) is recorded. The relative risk of the new development in the two categories is indicated simply by comparing the ratios of cases developed to men at risk in each category. If an infallible method was used to classify the men and no errors in diagnosis were made, the result of the computation is correct, but otherwise the computation will underestimate the true difference between the men in the two categories. A true correlation between the variable and ASHD will be reduced (attenuated) by any errors that may have been made.

Disregarding the question of diagnostic errors (which may not be negligible), it is possible to see what may be the effect of variability and errors of measurement of the variable on which classification was based. In regard to serum cholesterol, the analytical error in a good laboratory is small, the standard error of measurement being around ±5 mg. of cholesterol per 100 ml. of blood serum when duplicates of the same serum are independently analyzed.[23] But the variability between blood samples from the same individual is more important.

We, and others, have examined this question by analyzing blood samples drawn repeatedly under the same conditions from the same men at intervals of some days, weeks, or months.[23] Even when the men are apparently in a steady state of health and are adhering to a relatively constant mode of life, the variation in cholesterol values obtained is such that only about two thirds of the replicates fall within a range of ±20 mg. per 100 ml. from the mean of all values recorded from the individual (i. e., intra-individual standard deviation = 20). The variability undoubtedly would be greater if the sampling extended over longer periods of time and covered other than "standard" conditions.

All this means, of course, is that any classification of men in regard to cholesterol based on a single blood sample will result in errors in placing men according to their true individual mean cholesterol levels. The statistical implications of such considerations, and the mathematical theory involved, will be presented elsewhere.[24] The results indicate serious underestimates of the prognostic significance of the serum cholesterol level from the crude analysis of such data as are available from the Framingham and other prospective studies in which men were classified on the basis of a single blood sample.

Assuming an average intra-individual standard deviation of about 20 mg. per 100 ml., it appears that the men truly characterized by the upper 20 per cent of mean values for serum cholesterol at Framingham had a much greater risk, perhaps 60 to 70 per cent greater, than indicated from the original analysis. From the Albany data these considerations suggest that the risk of the men truly

averaging 275 or more mg. per 100 ml. was something like five to six times that of the men truly averaging less than 275.

The same considerations apply to measurements of relative weight and blood pressure, of course, but perhaps with less effect. Certainly a measurement of relative weight is subject to relatively little error and intra-individual variability and is therefore a more reliable estimate of the mean value for the individual than a measurement of serum cholesterol. And we suspect, though basic data are lacking, that the intra-individual variability in blood pressure may be less than that in serum cholesterol, at least if we refer to blood pressure under standardized conditions.

The conclusion from these considerations is that in regard to risk from ASHD the true predictive power of the relative weight is not much different from that indicated from the crude analysis based on a single measure. But the true predictive power of cholesterol, and perhaps that of the blood pressure, certainly must be underestimated from the data on single measurements in the Framingham, Albany, Los Angeles, and Cooperative studies.

Other Characteristics and the Risk of ASHD

This is not the place to discuss all characteristics that need consideration in regard to the risk of ASHD. Patients with various clinical diseases present different problems. Diabetic subjects are notably bad risks, atherogenesis is accelerated by nephrosis and, in spite of some controversy, probably also by deficiencies in thyroid and female sex hormones. It is significant that all these conditions involve alterations in cholesterol metabolism in the direction of hyper beta-lipoproteinemia.

In another category are variables about which there is more speculation than evidence, such as cigarette smoking and "tension" or emotional "stress." In some populations, at least, heavy cigarette smokers have an increased risk of ASHD but smokers have not been compared with nonsmokers in regard to other characteristics that may differentiate them. As for "tension" or "stress," there are no actuarial data, and the most persuasive evidence of a connection with ASHD risk is the indirect point that the serum cholesterol level is reported to rise under some conditions that are presumed to be stressful.

Risks and Conclusions about Causality

The relevance of all the foregoing to the first part of the questionnaire in our previous editorial is clear. Essentially, we asked opinions about the relative ASHD risk of men aged 40 who are overweight or have high blood pressure or hypercholesteremia. And, as indicated above, there *are* facts available on which to base such opinions.

But important, and indeed critical, questions remain. It is justifiable and useful to make statistical predictions from such evidence but drawing conclusions about causality is another matter. The fact that ASHD develops more often among men who are high in serum cholesterol or blood pressure does not necessarily mean that either of these characteristics actually causes the atherosclerosis and thrombosis we eventually observe. Nor does it follow necessarily that changing these characteristics toward more "favorable" values must, ipso facto, reduce the risk significantly.

While it is essential to recognize these limitations, it is also proper to insist that negative conclusions should be subjected to equally critical scrutiny. The absence of final positive proof of a hypothesis is not evidence that the hypothesis is false. Nor is it reasonable to conclude that the association between hypercholesteremia and ASHD does not involve causality simply because some obviously non-causal associations can be found between ASHD and some other variables.

This was the device used by Yudkin[25] to discredit epidemiologic evidence. He suggested that the frequency of ASHD in populations is related to the per capita use of telephones and radios and *therefore* the association observed between ASHD and other variables in populations is probably meaningless.

It is easy to suggest absurd analogies and we can do better than Yudkin on this score. There can be no question that ASHD is far more frequent among persons who shave daily than among those who never shave. But before advancing the proposition that shaving promotes ASHD or that stopping shaving may be prophylactic, we reflect that shavers are men and most nonshavers are women. Similarly, we can suggest that there may be good, i. e., understandable, reasons why populations that differ in their usage of telephones and radios would likewise differ in serum cholesterol or blood pressure.

The fact is that a good deal more is known about ASHD and the variables associated with it than the mere fact of the association observed epidemiologically. Among other things, it is unreasonable to disregard the findings in animal experiments, even though we debate as to how far these are directly relevant to the spontaneous disease in man.

When evidence from all sources is put together we can at least conclude that both experimental and epidemiologic findings are consistent with the hypothesis that ASHD in man is strongly promoted by hypercholesteremia and, perhaps to a lesser extent, by elevated blood pressure. The possible role of overweight or obesity as independent variables is far less clear. But even if the hypothesis of causality is accepted there still is no compelling reason to insist that treatment to reduce the cholesterol and blood pressure levels will produce a major change in the risk, especially in the middle-aged adult whose arteries are probably already half blocked with atherosclerosis.

Until now we have avoided defining hypercholesteremia and the general problem of "normal" and "abnormal." This merits a separate essay; but for the present purpose it is enough to consider the cutting points used in the several follow-up studies and the subsequent ASHD risk observed. We suggest that the definition of hypercholesteremia should be made in terms of relative risk. We might agree that serious hypercholesteremia would include cholesterol values associated with about three times the ASHD risk associated with lower values. Judging from the Cooperative and the Minnesota studies, this would mean, for American men, a boundary at something like 230 mg. of cholesterol per 100 ml. (to approximate the medians in those studies).

From the other studies, and consideration of intra-individual variability, we may defend the opinion that among clinically healthy middle-aged American men those who are truly characterized by cholesterol values of around 260 or more will have something like four or five times the ASHD risk of those with lower cholesterol values. Data from comparisons of populations here and abroad suggest that even a value of 220 mg. of cholesterol per 100 ml. might be set as a lower boundary for hypercholesteremia because above that level the risk of ASHD seems to be definitely increased.

Whether hypercholesteremia or elevated blood pressure or both should be treated in the hope of reducing the risk of ASHD is a matter of opinion involving considerations of safety, expense, and the difficulty for all concerned. Those who advocate treatment may do so in the knowledge that many other medical and hygienic customs are adopted and maintained on less secure grounds of scientific knowledge. But they, as well as the dissenters, should also know the available facts and their limitations.

ANCEL KEYS

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One still more recent change is observable relating to the current interpretation of disease. Quite significantly, our phraseology, which previously involved the word "disease," has begun to change, and we hear of health maintenance, health protection, and the health professions. This change signifies a larger horizon, a larger task, a larger number and variety of skills and personnel, but it also aims at a more positive and desirable goal than the mere absence of disease.—Alan Gregg, M.D., *Challenges to Comtemporary Medicine*. New York, Columbia University Press, 1956, p. 37.

Evaluation of the Surgical Correction of Mitral Regurgitation

By Earle B. Kay, M.D., David Mendelsohn, M.D., and Henry A. Zimmerman, M.D.

USUALLY the first questions to be asked by patients, their relatives, and their physicians, are: "What are the dangers of operation, and will it be a cure?" Obviously, any patient with rheumatic valvular disease will not be cured but may be given varying degrees of benefit dependent upon the degree of pathology, the degree of myocardial reserve, and the degree of effectiveness of the operative technic. The best results are obtained in good-risk patients who have less than severe cardiomegaly, reversible pulmonary vascular sclerosis, and a valvular mechanism amenable to correction. The myocardial component of valvular dysfunction cannot be overemphasized. No operative technic will be highly successful when employed in the presence of a failing heart. Similarly, the persistence of pulmonary vascular sclerosis may negate benefit gained by valvular correction.

Only too often in the past have physicians lost sight of the fact that cardiac disease is compensated at the expense of cardiac reserve. Only too often a patient with rheumatic valvular disease is followed medically until rapidly progressive deterioration becomes obvious, before surgical intervention is sought in the hopes of stopping this otherwise hopeless course.

In the past this policy has been justified in that surgical technics were not adequate to provide reasonable safety or assurance of benefit. The recent progress in surgical correction has now reversed this situation, so that safety and benefit are not so dependent upon the technic employed as they are on the time or state of the disease when surgery is performed.

Obviously, all patients with rheumatic valvular disease and specifically all patients with evidence of mitral regurgitation do not require operation. Many compensate for their disease and remain relatively stable for years. It is mandatory, however, for their physicians to recommend periodic examinations, and to determine from objective evidence of cardiac size and function whether the disease is progressive or stable.

Pathology

Twenty-three per cent of the regurgitant valves were of the pure variety in which the regurgitation was largely due to a disproportion between valvular tissue and annulus size so that the leaflets failed to approximate (fig. 1). A fourth of these patients had either disruption or stretching of the chordae tendineae with herniation of the leaflets into the atrium. The majority of these valves were repaired by variations of annular plication and resuturing or replacement of the chordae tendineae. These hearts had the greatest degree of myocardial hypertrophy. Several of the larger hearts of this group later stretched the valvular correction with recurrence of a regurgitant murmur.

Thirty-four per cent had combined, but predominantly regurgitant valves with an element of stenosis (fig. 2). Approximately 25 per cent of these had varying degrees of calcification. The heart size in patients with combined mitral stenosis and regurgitation was smaller than those with pure mitral regurgitation. There was considerable variation in the pathologic process causing the regurgitation, which necessitated individual adaptation of the operative technic. The majority were corrected with relative ease,

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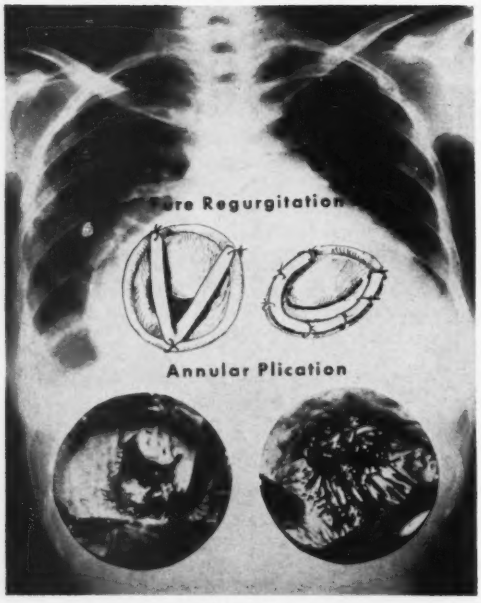

Figure 1

Example of roentgen and pathologic findings in patients with pure mitral regurgitation and the technic of annular plication employed for correction.

whereas others were corrected only partially and with difficulty.

In 29 per cent of the patients, the element of stenosis was greater than the regurgitation (fig. 3). These hearts were smaller than those in the first two groups. A large majority of the valves in this group were satisfactorily corrected.

The last group, with destroyed valves, comprised 14 per cent of the patients operated upon (fig. 4). In 11, the valvular destruction was due to extensive calcification detected in 10 instances preoperatively by image amplification or by over-penetrated roentgen examinations. In three, the valvular destruction was due to absorption and replacement of the valvular components by scar. These patients were by far the most seriously ill of all, and had persistent myocardial failure. Though we recognized preoperatively the critical risk involved, we elected to proceed in the hopes that some benefit could be afforded them. In nine, no worthwhile surgical correction short of valvular replacement could be obtained. All died postoperatively from myocardial failure.

Since the development of an artificial mitral valve, five have had valvular replacement. Though there have been no successful long-term survivors, the artificial valve appeared to function properly. The cause of death in two patients was from associated coronary occlusion with myocardial infarction; one was due to progressive myocardial failure in a patient operated upon 5 years previously for mitral regurgitation by one of the closed technics; one died 7 days postoperatively from renal failure while being perfused on the artificial kidney; and one died 14 days postoperatively from poor pulmonary function resulting from asthmatic bronchitis, emphysema, pulmonary vascular sclerosis, a refractory electrolyte imbalance, and myocardial failure. This patient also had been operated on 7 years previously. The gross appearance of the artificial valve in this patient is noted in figure 5. There were no complications relating to the valve.

The majority of the patients with valvular destruction (10 out of 14) were known preoperatively to be so involved and could have been denied a chance for help. It is our opinion that certain centers should continue their efforts to benefit this unfortunate group of patients, but that the poor results initially obtained should not unduly overshadow the good results in other patients.

Results in Relation to Valve Pathology

The results of surgical correction in relation to valve pathology are tabulated in table 1.

Pure Regurgitation

There was an over-all operative mortality during this 4-year period of 9 per cent. This was due mainly to air embolism occurring during the developmental stage of left-sided cardiotomies. This complication has been entirely corrected. One patient subsequently died suddenly 16 months postoperatively from acute rupture of the chordae tendineae.

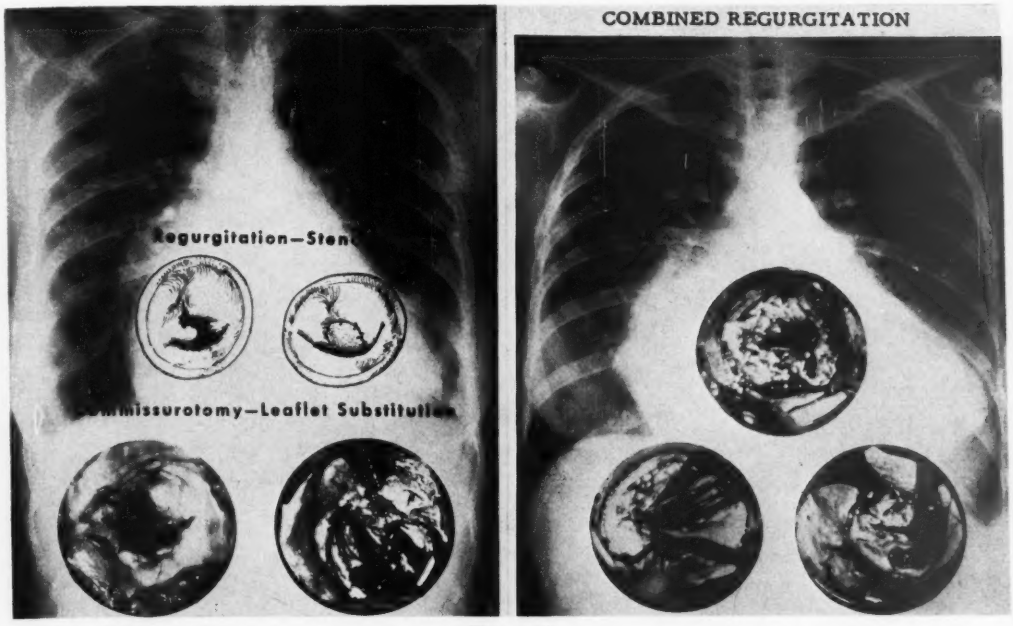

Figure 2

Examples of variations in valvular pathology in patients with combined but predominantly regurgitant lesions indicating valvular addition in the form of plastic material (left) *and selective annular plication at the posteromedial commissure* (right).

Table 1

Results in Relation to Valvular Pathology

Type	No.	Operative mortality		Status 6 mo.—3-1/2 yr.			
		No.	%	Dead	Fair	Good	
Pure regurgitation	23	2	9	1	4	16	80%
Predominant regurgitation	34	4	12	1	6	23	80%
Combined (predominant stenosis)	29	3	10			26	100%
Destroyed	14	14	100				

Table 2

One-Year Analysis of Patients Referred for Surgery

No.	Av. age	Failure	Size		Av. Press. mm. Hg		Pathology		Result
			M	S	PA	PC	D	C	
6	47	100%	17	83	74	28	1	3*	Died preop.
8	43	100%	12	88	76	37	5†	3	Died preop.
4	34	100%	25	75	40	28	1	3	No improvement 1 Partly improved 3
23	39	34%	78	22	56	24		23	Improved

*Autopsies not obtained on two patients. Two valves replaced with artificial valves.
†M, moderate; S, severe; D, destroyed; C, corrected.

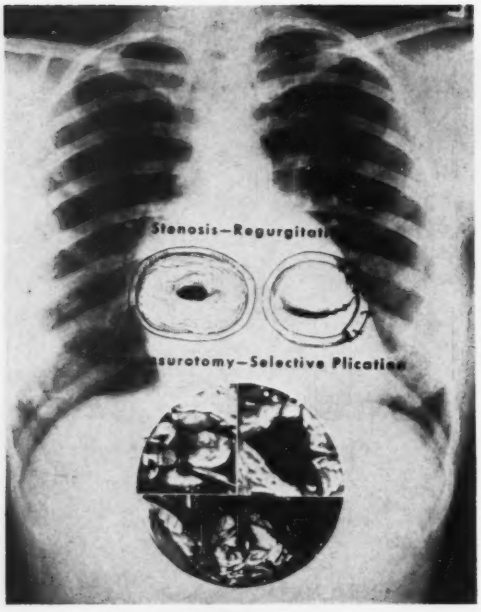

Figure 3

Example of valvular pathology in patients with combined but predominantly stenotic lesions indicating type of correction employed.

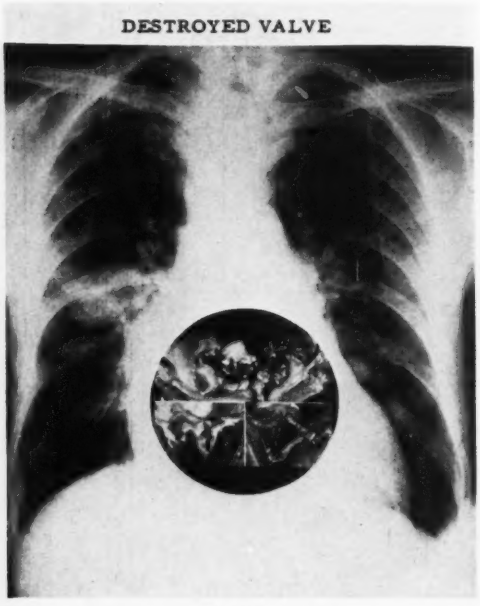

Figure 4

Examples of valvular pathology encountered in destroyed valves either by calcification or scirrhous replacement of the valvular components.

Until then he had been doing well. Of the surviving 20 patients, 20 per cent have had fairly good results. All had grade-IV cardiomegaly. In three, subsequent stretching of the surgical correction by hypertrophied myocardium caused the regurgitation to recur. Subsequent modifications of the operative technic have largely solved this complication. Earlier intervention in the future before grade-IV cardiomegaly develops, may also eliminate this problem. A possible endocarditis in a fourth patient may have compromised the surgical correction. Eighty per cent of the surviving patients have continued to do well from 6 months to 3½ years following surgery.

Predominant Regurgitation

There was an operative mortality of 12 per cent, due to early technical complications, incomplete surgical correction, and myocardial failure. One patient died 6 months postoperatively from myocardial failure. Of the 29 surviving patients, 20 per cent had fair response. Failure of greater benefit was due to poor myocardial reserve or to incomplete surgical correction. Greater benefit may be forthcoming in the future if valvular replacement proves effective. Eighty per cent of the patients received considerable benefit.

Predominant Stenosis

There was an operative mortality of 10 per cent. There were no intervening deaths during this 3½-year period. All surviving patients continued to do well during this period of evaluation.

A better understanding of the results of surgery in the treatment of mitral regurgitation can be obtained by an analysis of 41 consecutive patients being referred for operation over a 12-month period. These were patients who had been evaluated 2 or 3 months previously and who were considered at that time to be suitable candidates for surgery. They can be classified into four groups: Group I, six patients admitted to the hospital in the hope of surgical relief

Table 3

Results Based on Clinical Evaluation

Year	No.	Status Oct. 1960			
		Dead	Fair	Good	
1957	5		1	4	(80%)
1958	20	2 (6 mo.) (2 yr.)	2	16	(80%)
1959	32	0	5	27	(84.4%)
1960 (6 mo.)	18	0	3	15	(83.3%)

who deteriorated and died prior to surgery; Group II, eight patients who underwent surgery but failed to survive, largely due to insufficient myocardial reserve; Group III, four patients who obtained only partial benefit from surgery; and Group IV, 23 patients who were significantly improved following surgery (table 2).

It is readily apparent from table 2 that the patients who died immediately prior to and following surgery were the ones most severely disabled from their disease and who had greater degrees of cardiac failure, cardiomegaly, altered hemodynamics, and pulmonary vascular sclerosis. They were also in an older age group and had a higher incidence of destroyed valves with coexistent artery disease.

During this 12-month period the preoperative mortality was almost as high as the postoperative mortality. The operative mortality would have been lower had we not chosen to proceed with operation in four of the five patients with destroyed valves who were known preoperatively to have extensive calcification of their mitral valves. The higher operative mortality in obviously high-risk patients should not deter physicians from recommending operation in good-risk patients who would have a much lower operative risk.

Results Based on Clinical Evaluation

Evaluation of results in patients surviving operation as based on clinical appraisal 6 months to 3½ years postoperatively is presented in table 3. The benefit obtained in the majority of patients corrected by means

Figure 5

Gross appearance of mitral prosthesis in patient dying 14 days postoperatively from multiple complications. During this period of time the valve functioned properly and there were no complications relating to its use.

available through the open approach has continued to warrant our enthusiasm. Two patients (3 per cent) have died during this 4-year period following surgery as noted previously. This small mortality is considerably less than that seen in unoperated patients. In the eleven (15 per cent) doing fair to fairly well, four had valvular mechanisms for which maximal correction could not be obtained. The other seven patients had large hearts with lessened degrees of myocardial reserve. Though the degree of improvement is certainly less than desired, the majority are out of failure and are able to perform most of their duties.

Eighty-two per cent of the patients are continuing to do well from 6 months to 3½ years postoperatively. The degree of improvement was proportionate to the degree of cardiopulmonary damage existing at the time of the operative procedure. Modifica-

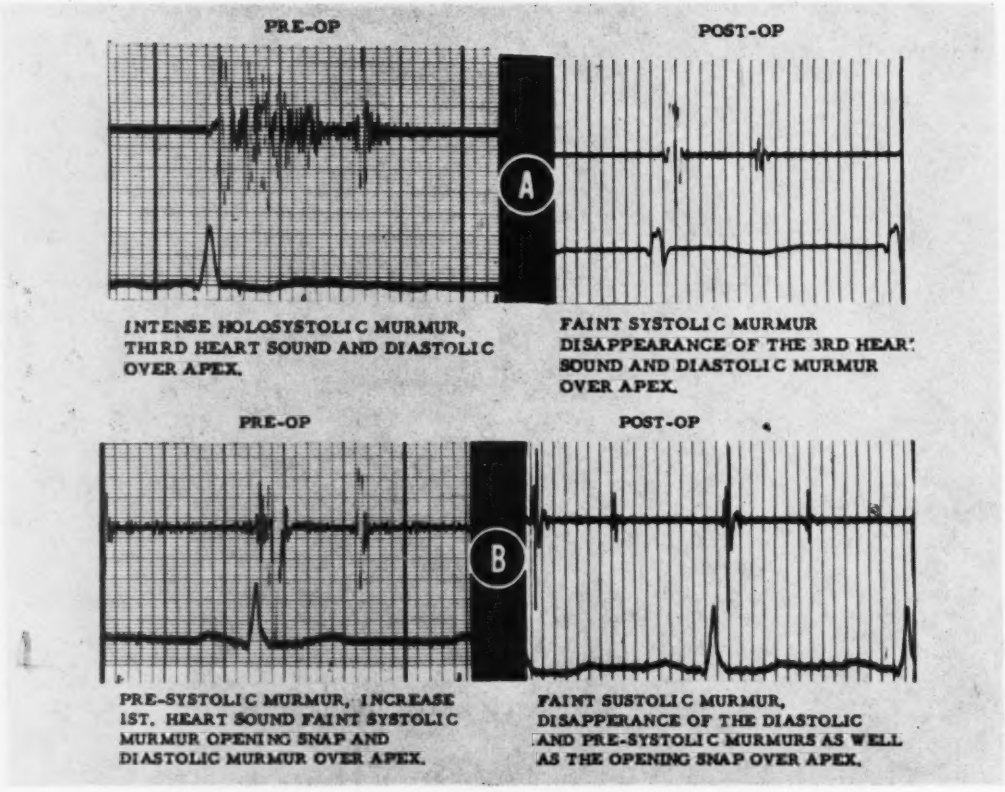
PRE-OP
POST-OP
A
INTENSE HOLOSYSTOLIC MURMUR, THIRD HEART SOUND AND DIASTOLIC OVER APEX.
FAINT SYSTOLIC MURMUR DISAPPEARANCE OF THE 3RD HEART SOUND AND DIASTOLIC MURMUR OVER APEX.
PRE-OP
POST-OP
B
PRE-SYSTOLIC MURMUR, INCREASE 1ST. HEART SOUND FAINT SYSTOLIC MURMUR OPENING SNAP AND DIASTOLIC MURMUR OVER APEX.
FAINT SUSTOLIC MURMUR, DISAPPERANCE OF THE DIASTOLIC AND PRE-SYSTOLIC MURMURS AS WELL AS THE OPENING SNAP OVER APEX.

Figure 6

A. Preoperative and postoperative phonocardiograms illustrating disappearance of the systolic murmur characteristic of mitral regurgitation following surgical correction in a patient with pure mitral regurgitation. B. Preoperative and postoperative phonocardiograms illustrating disappearance of murmurs following correction in a patient with combined but predominant stenosis.

tions and improvements in the surgical technic have increased the effectiveness of the surgical correction.

Results in Reference to Cardiomegaly

Cardiomegaly is a factor in operative mortality as well as operative result. It is also a factor in the higher incidence of postoperative pulmonary complications as a result of the mechanical interference with ventilation. Cardiomegaly is an indication of decreased myocardial reserve. Partial recurrence of the regurgitation was seen more often in the presence of severe cardiomegaly. The majority of patients with pure and predominant mitral regurgitation have had some reduction in heart size postoperatively, due largely to reduction of the cardiac dilatation. It is anticipated that the mass of myocardial hypertrophy existing over a number of years will decrease slowly with the lessened burden following correction.

Electrocardiographic Findings

The electrocardiographic pattern closely parallels the roentgen findings; the greater the abnormality preoperatively, the greater the findings are postoperatively. Though 70 per cent of the patients with atrial fibrillation have converted to normal, there has

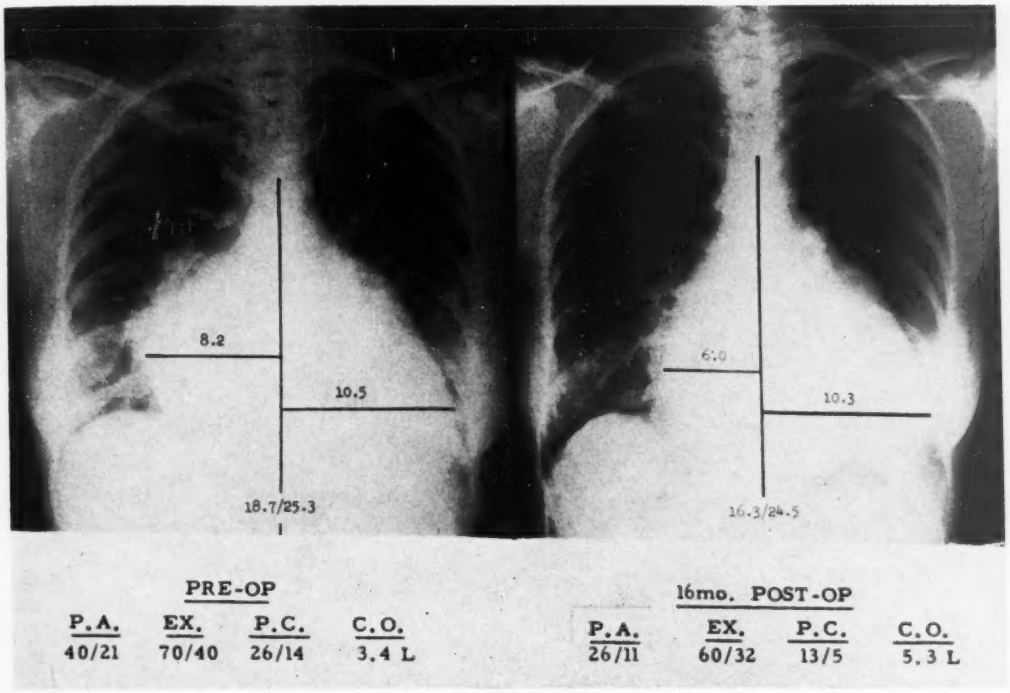

Figure 7

Demonstrates good roentgen and hemodynamic improvement in a patient with pure mitral regurgitation.

been little change in the pattern of left ventricular overload.

Murmurs

The best method to correlate change before and after operation or improvement in the character of a murmur is by phonocardiographic examinations (fig. 6). The majority of patients with pure mitral regurgitation had either no systolic murmur or only a slightly detectable one in the immediate postoperative period. In 3 or 4 months a systolic murmur was evident in five patients with large hearts. Over two thirds of the patients had a definite change in the character of the murmur that suggested improvement.

Table 4

Hemodynamic Evaluation

Type	No.	Hemodynamic	Clinical			
			No.	Fair	Good	
Pure regurgitation	10	No change	4	1	3	
		Improved	1		1	60%
		Normal	5		5	
Predominant regurgitation	9	No change	3	0	3	
		Improved	6		6	66%
		Normal				
Combined (predominant stenosis)	12	No change				
		Improved	4		4	100%
		Normal	8		8	

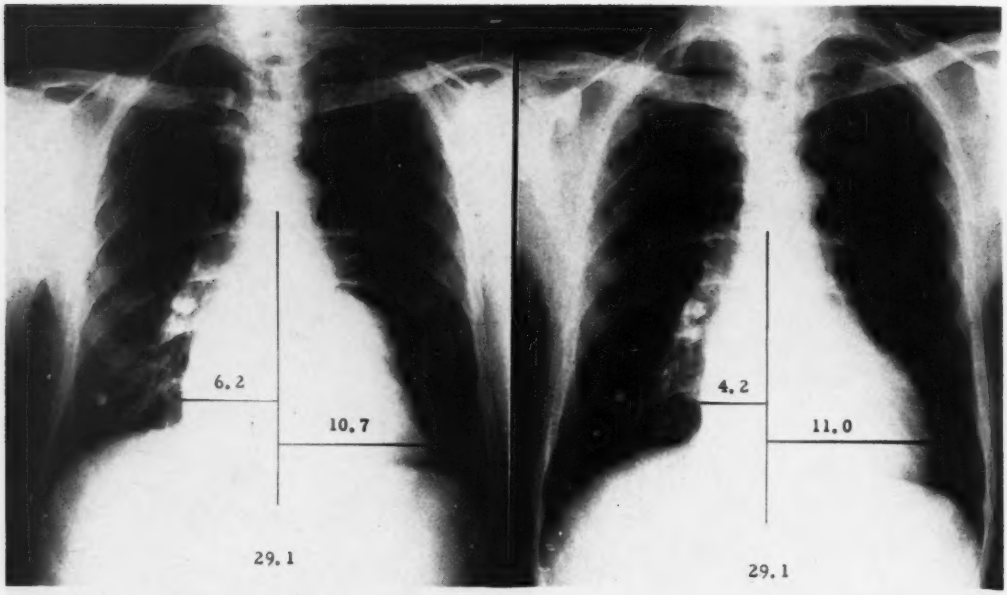

Figure 8

Demonstrates excellent roentgen and hemodynamic improvement in a patient with pure mitral regurgitation.

In the other third the murmur was only questionably detectable. The presence and character of the murmur are largely correlated with the degree of cardiomegaly. Murmurs are more likely to be absent or markedly diminished in those patients with smaller hearts.

Approximately 10 per cent of the patients had a febrile episode postoperatively. Though the etiology could not be determined with certainty, bacterial endocarditis was suspected. The recurrence of murmurs occasionally followed this complication. The majority of patients with combined but predominant mitral regurgitation had persistence of the murmur, though markedly changed in character. Less change in the character of the murmur was noted in patients with valvular calcification. In contrast, the majority of the patients with combined regurgitation but predominant stenosis had marked improvement in the character of the murmur, and in many instances the murmurs were hardly detectable.

Hemodynamic Findings

Thirty-one patients were studied by catheterization after operation (table 4). Their findings have fallen into three groups: (1) those with no significant hemodynamic improvement, (2) those with significant improvement, and (3) those that returned to essentially normal hemodynamic levels.

Pure Regurgitation

There were four patients in the first group, all of whom had severe cardiomegaly. In two instances the murmur indicative of mitral regurgitation after 1 to 2 years was still absent but catheterization studies showed no reduction in either pulmonary artery or

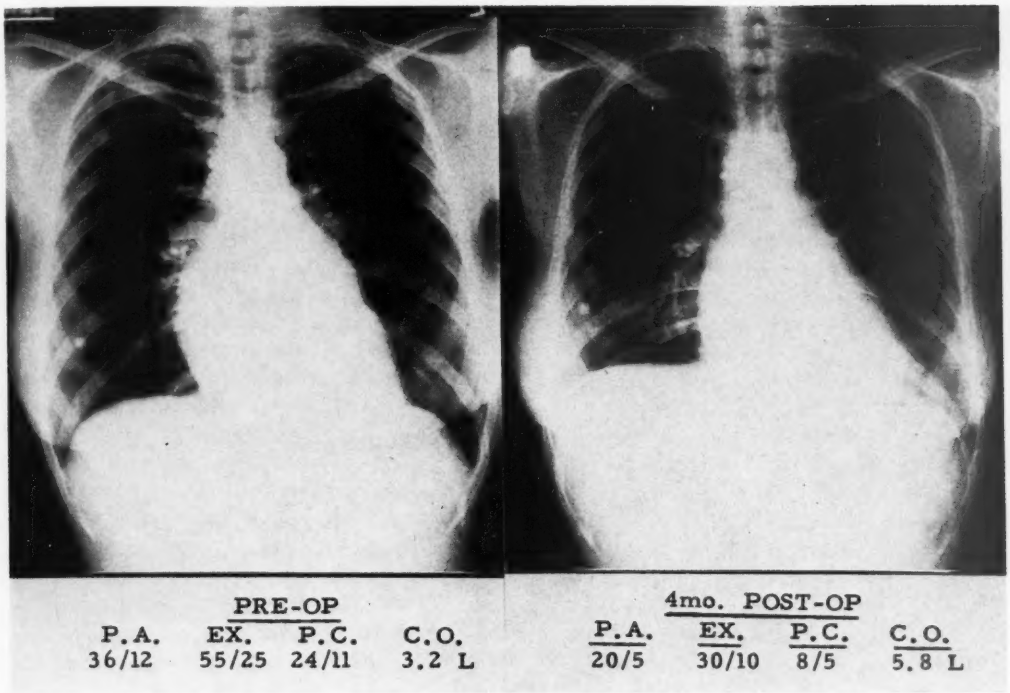

Figure 9

Demonstrates roentgen and hemodynamic improvement in a patient with combined but predominant stenosis.

wedge pressures. One of these patients had only fair clinical improvement. The other three had considerable improvement over preoperative status.

One patient had both clinical and hemodynamic improvement. As demonstrated in figure 7 the resting pulmonary artery pressures, as well as the pulmonary wedge pressures, returned to normal but the pulmonary artery pressure with exercise was still elevated, which suggested that significant pulmonary vascular sclerosis was still present 16 months postoperatively.

Five patients had returned to normal pressures (fig. 8). These patients had smaller hearts than those in the above two categories.

Predominant Regurgitation

Nine patients had postoperative catheterization studies. In three there was no significant reduction in hemodynamic abnormalities, although clinically they have done well. Six patients had significant reduction in catheterization abnormalities. It may be that these studies performed on the average of about 1 year following surgical correction were performed too soon to allow pathologic changes to be reversed. This was suggested by one patient having studies performed 6 months and again 1 year following correction. The preoperative pulmonary artery pressures were 80/35 mm. of Hg, with a wedge pressure of 56/27 mm. of Hg. Six months postoperatively the pulmonary artery pressures had reduced to 67/30 mm. of Hg, and the wedge pressure to 40/20 mm. of Hg. At the end of a year the pulmonary artery pressure had fallen to 55/15 mm. of Hg.

Predominant Stenosis

All of the patients with predominant stenosis but with some element of regurgita-

tion had both clinical and hemodynamic improvement (fig. 9).

Discussion

It is still too soon to present a valid opinion as to the lasting benefit of the original correction of mitral regurgitation. The benefit derived, however, in the majority of patients during this 3½ year period lends enthusiasm to the surgical approach to this otherwise progressively deteriorating disease. Further improvement in surgical technic will undoubtedly add to the effectiveness of the procedure. An analysis of the patients and their response to surgical therapy suggests that benefit derived is largely related to the status of the myocardium at the time of the surgical intervention and that greater help could have been provided if the operative correction had been performed when it became obvious that the pathologic process was progressive, rather than delaying until it was quite apparent that surgical help was mandatory.

On Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves

By DOMINIC JOHN CORRIGAN, M.D.

One of the Physicians to the Charitable Infirmary, Jervis Street, Dublin; Lecturer on the Theory and Practice of Medicine; Consulting Physician to St. Patrick's College, Maynooth.

. . . In the perfect state of the valvular apparatus at the mouth of the aorta, the valves support by intervals the column of blood in the aorta, and the heart with its ordinary complement of fibre and of muscular strength, is with this assistance competent to the office it has to perform. But when, in consequence of a deficiency in the valvular apparatus, the heart does not receive its due share of assistance from these valves, and is obliged to perform not only its own function of propelling the blood, but has in addition to support after each contraction a portion of that weight of blood which should then be wholly supported by the valves, it is no longer in its ordinary state equal to the task imposed upon it. In such circumstances, nature, to enable the heart to perform the additional labour thrown on it, increases its strength by an addition of muscular fibre, and the heart thus becomes hypertrophied, in accordance with the general law, that muscular fibres become thickened and strengthened when there is additional power required from it. Is this hypertrophy disease, or is it a wise provision of nature, by which the organ is thus made equal to the increased labour it has to perform? On the answer depends the treatment to be adopted; and on this there is no room for hesitation. A heart of ordinary strength could not, under the circumstances, carry on the circulation; and nature then wisely endows the heart with the requisite degree of strength. It is at once obvious that to interfere with this wise provision of nature, to diminish the strength of the heart, or, if we choose other words, to direct, according to the advice of Laennec, Bertin, etc. our measures against the hypertrophy of the organ, is to deprive the system of the only power which enables the heart to carry on the circulation.

Stenosis of Left Ventricular Outflow Tract

Causes and Contrast Visualization

By CHARLES T. DOTTER, M.D., J. DAVID BRISTOW, M.D., VICTOR D. MENASHE, M.D., ALBERT STARR, M.D., AND HERBERT E. GRISWOLD, M.D.

AMONG the several pathologic entities capable of presenting the clinical syndrome of aortic stenosis are congenital and acquired aortic valvular stenosis, supravalvular and subaortic stenosis, and muscular hypertrophy of the left ventricular outflow tract. Differentiation of the responsible lesion has become a clinical necessity since surgical measures are often indicated. Knowledge of the site, character, and hemodynamic consequences of the obstructing lesion makes possible the competent selection of surgical candidates and permits advanced planning of an operative attack appropriate to individual circumstances. In the following survey of aortic stenosis and related obstructing lesions, particular attention is given to the critical diagnostic roles of selective left heart visualization and manometric studies.

Radiologic contrast visualization provides a means for inspecting the functioning left ventricle, aortic valves, and thoracic aorta. In certain respects it is superior to direct examination. Chief among these is the advantage of studying undisturbed structures under relatively normal functional circumstances.

During the past quarter century of experience with contrast cardiovascular visualization many technics have been proposed for left heart visualization. If the ineffective and unduly hazardous ones are disregarded, several different approaches remain.[1] Regardless of the method employed, success in contrast visualization requires that an adequate concentration of contrast agent be so placed (in space and time) as to allow the desired radiographic study. Direct injection into the left ventricle is essential to the study of the left ventricular outflow tract. Conventional intravenous angiocardiography and selective catheter injections into the right heart or pulmonary arteries are not satisfactory for this purpose because of dilution and other factors. Occasional brilliant exceptions are unfortunately out of context. The amount and time of injection, route of administration, and the time, duration, and frequency of x-ray exposures are best determined on the basis of the patient's anatomy and physiology rather than by arbitrary standards.

Percutaneous retrograde catheterization of peripheral arteries permits the insertion of large-bore polyethylene tubing into the left ventricle and thereby makes possible both contrast visualization and manometric studies. Based upon the pioneer contributions of Seldinger[2] and Prioton and associates,[3] a technic employing a flexible coilspring guide has been used successfully in over 300 patients at the University of Oregon Medical School.[4, 5] The safety of the technic has allowed its use in outpatients, and its simplicity is evidenced by the usual achievement of left ventricular catheterization within 5 or 10 minutes after starting the arterial puncture. Unquestionably, aortic valvular stenosis increases both the need and the difficulty of transvalvular catheterization; fortunately it rarely prevents the accomplishment.

In brief, the technic begins with needle puncture of a femoral or other peripheral artery under local anesthesia. A 125-cm. long, flexible coilspring guide, resembling a guitar string and containing a piano-wire stiffner, is inserted into the arterial lumen through the

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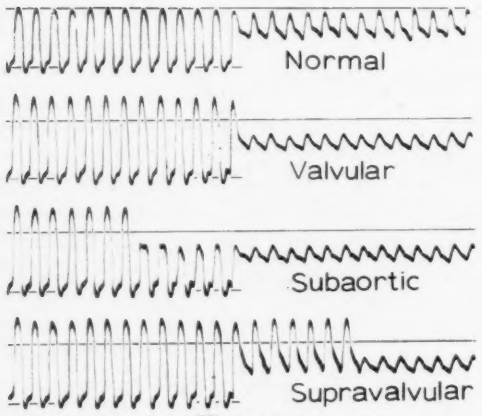

Figure 1

Blood pressure findings in aortic stenosis. Redrawn "ideal" records. Upper line on each trace represents normal systolic level. Normally, left ventricular and aortic pressures are the same. In aortic valvular stenosis there are left ventricular hypertension and a significantly lower systolic pressure in the aorta. The drop in pressure is a guide to the severity of the lesion, whereas the location of the gradient indicates the anatomic site. Gradients are best considered in relation to the maximum systolic pressure rather than as absolute figures, since they are greatly influenced by stroke volume and heart rate.

needle. The latter is then withdrawn and removed by sliding it along and off the guide, which is kept in place. Suitable length of polyethylene tubing, usually PE 240, is next slipped sleeve-fashion over the guide and advanced until, with a rotary motion, its tip enters the arterial lumen. The tubing is shorter than the spring guide by a known amount, so that the relative positions of tubing and guide may be adjusted after their insertion.

Fluoroscopy is used during placement of the catheter, manipulation of which is generally best accomplished with 2 or 3 inches of guide protruding from the exploring end of the tubing. The major branches of the abdominal aorta, and brachiocephalic and coronary arteries can usually be entered as desired. Retrograde transvalvular passage is favored by the formation of a partial loop in the flexible protruding end of the guide following its impingement on an aortic valve cusp. Entry into the ventricle is effected when an appropriate combination of valve action and catheter manipulation allows the loop to snap straight. At this juncture ventricular extrasystoles are usually noted on the monitoring cathode-ray oscilloscope. The polyethylene tubing is advanced along the guide into the desired location in the ventricle, and the guide is withdrawn to allow manometric study and the injection of contrast substance. Slight manipulation of the catheter will usually result in obtaining a position unassociated with ectopic beats.

After observation and recording of intraventricular pressure, contrast agent (amounting to about half of the patient's estimated resting stroke volume) is delivered by means of a pressure injector.[6] Rapid serial radiographic exposures are made for 4 to 6 seconds from the start of the injection. The left posterior oblique projection (approximately 35 to 40° rotation) provides a satisfactory view of the left ventricle as well as its mitral and aortic valves.

With the pressure-recording system operating, the catheter is withdrawn until its tip lies above the level of the coronary arteries within the proximal aorta. Pressure curves indicate when a supravalvular position has been achieved, but—in children at least—it may be wise further to confirm the catheter location by fluoroscopy, 1 or 2 ml. of contrast substance being injected into the otherwise radiolucent polyethylene catheter. The inadvertent injection of the aortic dose of contrast substance into a carotid, vertebral, or coronary artery is the major hazard of this technic. Fortunately, it is readily avoided by careful technic. Filming of the supravalvular contrast injection is best carried out with the patient in the right posterior oblique projection (60 to 80° rotation). As soon as the blood pressure has stabilized, the catheter is withdrawn during continuous pressure recording, and a sterile hemostatic pressure dressing is applied over the femoral puncture.

Observation of intraventricular and intraaortic blood pressures usually establishes the diagnosis of stenosis of left ventricular outflow

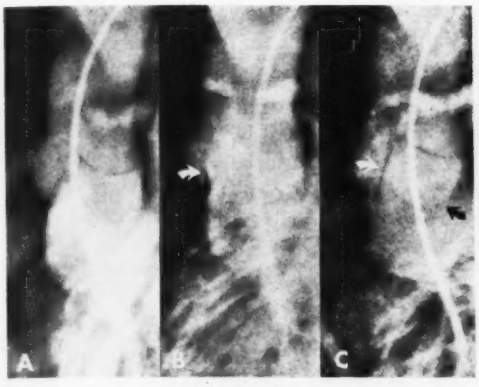

Figure 2

Normal aortic valve. During diastole (A *and* C), *two of the aortic leaflets are profiled as thin, uniformly thick curved lines that continue the contour established by their respective sinuses of Valsalva and meet centrally* (white arrows in C). *The third cusp is usually visible* (black arrow in C). *During systolic ejection* (B) *the cusps are normally more difficult to identify but often one or two are shown, at least in their proximal portions, as vertically oriented shadows roughly parallel to the aortic walls* (white arrow in B). *Difficulty in visualizing the free margin is due to motion. Note also the varying appearance of the normal subvalvular infundibulum of the left ventricle.*

Figure 3

Congenital valvular aortic stenosis: classical appearance. Percutaneous transfemoral catheterization supravalvular injection. In diastole (A), *a relatively normal appearance is presented though the individual sinuses of Valsalva are somewhat small. Although no diastolic murmur was noted, there is a subvalvular puff of contrast agent indicating adynamic aortic insufficiency. Markedly different during systolic ejection* (B), *the upward ballooned, unsegmented aortic valve forms a dome through which may be seen to issue an eccentrically directed jet of radiolucent blood. Trans-stenotic pressure gradient was considerably reduced by surgery.*

tract early in the procedure (fig. 1). When ventricular irritability occurs as the catheter is withdrawn from the ventricle, a subvalvular chamber may not be represented faithfully in the pressure record. The differentiation of pressure changes due to valvular artifact, premature ventricular contractions, or a small chamber above or below the valve may be difficult or impossible. The interpretation of pressure records is also complicated by the use of side-holes near the catheter tip designed to prevent catheter recoil during injection. Nevertheless, pressure studies provide important information concerning the presence and severity of trans-stenotic pressure gradients and, at present, are regarded as indispensable in the selection of patients for surgical correction. Inasmuch as the actual site of the stenosis and other valuable anatomic information are demonstrable by angiography, it is fortunate that both types of information can be gained with a single precedure.

Valvular Aortic Stenosis

Isolated aortic valvular stenosis in adults has been ascribed to degenerative sclerosis, rheumatic infection, and congenital aortic disease. Coexistent mitral disease offers strong, if circumstantial, evidence of rheumatic origin. In its absence and without a history of rheumatic fever, the presumptive diagnosis of congenital aortic stenosis is preferable, particularly in young patients. Since calcification may develop in congenitally stenotic valves (it has been observed in patients as young as 18), calcification per se offers no support for the diagnosis of rheumatic aortic stenosis. There remains uncertainty about the cause of the disease, particularly in older patients—a doubt shared by pathologist and clinician. In any event, if rheumatic carditis is excluded, the etiology probably does not influence prognosis or therapy.

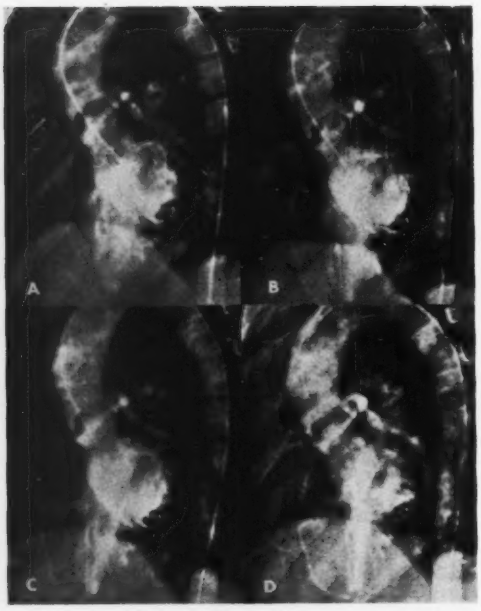

Figure 4

Congenital valvular aortic stenosis: rigidity. The four sequential views here reveal a thickened dome that does not preceptibly change its position during various phases of the cardiac cycle. The left ventricular-aortic systolic gradient was 124 mm. Hg.

Children with congenital lesions may experience angina, syncope, and heart failure. Sudden death as a complication of aortic stenosis is said to be frequent. In adults, the disease is reported to have been associated with sudden death in one out of every four autopsied cases. The classical symptoms of syncope, effort intolerance, dyspnea, and other manifestations of heart failure are well known. In adults, angina often indicates coexistent coronary arteriosclerosis. In this unfortunate and highly lethal combination, two distinct anatomic limitations additively oppose the increase in coronary flow demanded by the ventricular hypertrophy that results from the valvular obstruction. Life expectancy in such patients bears a direct relationship to the heart's continuing ability to hypertrophy.

In severe aortic stenosis, regardless of the etiology, the peripheral pulse characteristically exhibits a low amplitude and prolonged rise-time, but this is not always so. Generally, the systolic blood pressure is below 140 mm. Hg but, again, exceptions have occurred. Usually aortic stenosis is associated with a systolic thrill at the base of the heart. A palpable increase in the left ventricular impulse is another commonly encountered physical sign in aortic stenosis and related obstructive lesions of the left ventricular outflow tract. The sine qua non of the clinical diagnosis is a loud systolic ejection murmur. Its point of maximum intensity is most often in the aortic area, but it can be at the apex. Appraisal of the relative intensities of the two valve-closure sounds and the modifications in their response to respiration are of value. A soft, or silent aortic closure is often but not always found in patients with aortic stenosis, whereas paradoxical splitting of the second sound is a common finding believed to be constant in severe stenosis.

Aortic diastolic murmurs are often heard in patients with aortic stenosis. It is clearly of clinical significance when due to aortic regurgitation of such a degree as to cause a diastolic thrill or the physical signs of abnormally high aortic run-off. Even in the absence of a diastolic murmur, associated aortic regurgitation of very slight degree may result in catastrophe during attempted open-heart surgical repair without coronary perfusion.[7] Aortography not only can identify subclinical aortic regurgitation, it can exclude it.

The left ventricular enlargement that occurs in any type of aortic stenosis may be demonstrated by conventional radiologic and electrocardiographic technics. Hypertrophy without dilatation of the left ventricle is common in the absence of heart failure or associated aortic or mitral insufficiency. Dilatation of the ascending aorta is a frequent manifestation of post-stenotic turbulence when obstruction antecedes the loss of aortic elasticity. It is also seen in aortic insufficiency without stenosis, syphilitic aortitis, hypertension, Marfan's syndrome, coarctation of the aorta, aorticopulmonary defect, common

truncus, and other conditions including nonvalvular congenital aortic stenosis. Like most of the findings already mentioned, aortic dilatation is at most confirmatory evidence of aortic valve narrowing. Considered in concert, the signs and symptoms of aortic valvular stenosis enable reasonably accurate diagnosis but it remains for left heart catheterization to provide essential knowledge of the individual anatomic changes and resultant transstenotic pressure gradient in blood pressure.

Pressures recorded from the left ventricle and proximal aorta provide quantitative data concerning the hemodynamic effects of aortic stenosis and guides to the adequacy of its surgical correction. In our opinion, surgery is indicated when noncalcific aortic stenosis without significant aortic insufficiency has caused the left ventricular systolic pressure to exceed that in the aorta by more than 50 mm. Hg. It is far more difficult to assess the hemodynamic importance of aortic stenosis when mitral disease is also present. A resultant reduction in effective stroke volume may lower aortic valve gradients deceptively.

Contrast visualization of the left ventricle and aortic valve is indispensable to the competent preoperative work-up of patients with stenosis of left ventricular outflow tract. Adequate studies can be depended upon to reveal the structure and cyclic variations of the left ventricle, aortic valve, and proximal aorta. Directional and quantitative information about blood flow is also obtained and mitral insufficiency may be identified or excluded.

Identification or exclusion of aortic insufficiency may similarly be accomplished by means of supravalvular aortic injections. Here also, careful attention to technical details such as the orientation of the catheter tip will permit reliable conclusions. Clinically appreciable aortic regurgitation always results in radiologically visible retrograde passage of contrast agent through the abnormal valve into the left ventricle. When there is regurgitation sufficient to produce clinical evidence of functional impairment, the entire ventricle fills. In the functionally

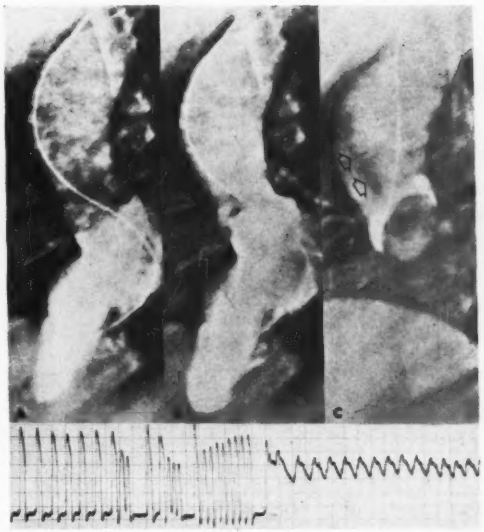

Figure 5

Congenital aortic valvular stenosis: early secondary degenerative change. Left ventricular injection, A, *during diastole;* B. *during systole. The latter shows eccentric thickening of valve cusps and moderate dilatation of the poststenotic aorta.* C, *during ventricular systole following supravalvular injection shows dome-shaped valve and jet of nonopaque blood in aorta, indicating small size and off-center location of orifice. Pressure record (below) during withdrawal of catheter from left ventricle to aorta. The gradient was approximately 50mm. Hg. At surgery, incomplete segmentation of the right and posterior cusps was found with fibrosis and calcification at commissural site and also incomplete separation of right and left aortic cusps.*

unimportant regurgitation, which often accompanies nonrheumatic aortic stenosis, there is apt to be a more transitory subvalvular puff of contrast agent. Functionally important aortic insufficiency produces other gross angiographic findings.

With supravalvular contrast injections the normal aortic valve is seen as a trilobulate expansion of the root of the aorta. The three dilatations are the shadow of contrast agent within the sinuses of Valsalva and are roughly equal in size. Films exposed during ventricular ejection usually show an irregular interface between radiolucent blood and contrast agent in the aorta. Estimates of the volume

Figure 6

Congenital valvular aortic stenosis: degenerative change and eccentricity. Supravalvular injection reveals marked distortion of the sinuses of Valsalva. One large, evidently quite flexible valve cusp is present. Blood reaches the aorta through the eccentric orifice at the site of calcific deposits seen fluoroscopically. Pressures at time of visualization were left ventricle 210/10, thoracic aorta 140/90. Following surgery these fell to 150/5 and 140/110 respectively.

of ejection by measurement of the radiolucent area have serious shortcomings. When contrast agent is injected into the left ventricle and radiographs are exposed during diastole, two of the three aortic cusps are often outlined in profile while the third is outlined *en face* by a contrast agent in its respective sinus. The normal aortic valve leaflets are symmetrical, smoothly contoured, evenly thin in radiographic cross section, and flexible as judged from exposures made during various phases of the cardiac cycle. In systole, the cusps are not as readily outlined because of their motion (best results are obtained through the use of short exposures). Often one or two of the cusps may be recognized as a short radiolucent line extending upwards from the point of attachment for a distance of about

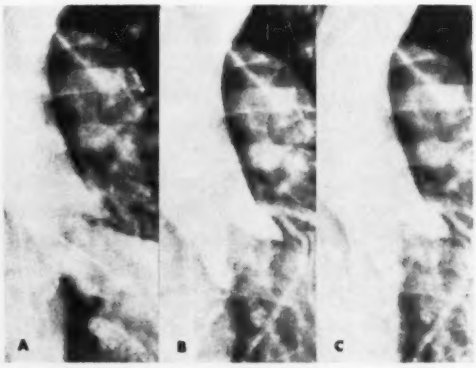

Figure 7

Rheumatic aortic valvular disease, predominant stenosis. A. *Left ventricular injection of contrast agent.* B *and* C. *Supravalvular injection. The aortic valves are thickened, straightened, and quite rigid in all phases of cardiac cycle. The appearance is more like that of a tent than the rounded dome in early congenital stenosis. Despite chronicity of the disease process, the abnormal valve is more or less symmetrical in appearance. Moderate aortic regurgitation is demonstrated. The shadow of a thickened mitral valve is seen in A.*

half the length of the cusp; motion or superimposed contrast agent obscures the free edge. The characteristic configuration of the normal aortic valve is well shown in figure 2.

When valvular stenosis is present, selective contrast visualization regularly demonstrates gross and characteristic abnormalities of the valve leaflets (figs. 3 to 8). In the absence of degenerative changes, congenital aortic stenosis is most commonly seen as a curved radiolucent line with convexity directed upwards. This is the cross sectional shadow of the dome formed by the incompletely segmented cusps and is usually best shown during systolic ejection. When contrast agent is injected above the stenotic valve, the latter outlines a rounded radiolucent defect at the base of the aorta. Diastolic exposures often reveal a surprisingly normal appearance although there is likely to be flattening of the sinus pockets. Figure 3 shows the striking systolic-diastolic variation that occurs in the still flexible, but congenitally unsegmented, stenotic aortic valve. That the dome in congenital aortic stenosis may be rigid is illus-

trated in figure 4. Diastolic exposures during supravalvular injections are most likely to reveal relatively minor aortic regurgitation but it should be noted that impingement of the catheter tip or the jet issuing from it can simulate regurgitation. In congenital aortic stenosis, supravalvular injection often reveals radiolucent blood spurting through the stenotic orifice and gives rise to what might best be described as a systolic jet sign. This filling defect is narrow at its base and frequently is eccentrically located. The extent to which its axis deviates from the central axis of the aorta probably correlates with the presence of superimposed sclerotic change. The distortion and rigidity that accompany sclerotic degeneration (evidenced by calcification, age, rheumatic origin) are less likely to be associated with the jet sign. Instead, the films disclose asymmetric thickening, rigidity, and irregularity of the valve cusps (figs. 4 to 6). Asymmetrical involvement is not rare and, as shown in figure 6, may be associated with both an eccentric orifice and an abnormally large single sinus of Valsalva. Despite what appears to be prolapse of the relatively normal single cusp, we have not observed gross insufficiency in this situation. The large, flexible, relatively unaffected cusp may be used to achieve a competent valve in conjunction with surgical relief of the stenosis.[8] Figure 7 shows a rigid, stenotic, incompetent but symmetrical valve in rheumatic heart disease of long standing. It also shows rigidity and calcification of the mitral valve. In figure 8, the lesion of rheumatic aortic stenosis and insufficiency was also relatively symmetrical. On the basis of these studies the superimposition of sclerotic degenerative change on a congenitally stenotic aortic valve seems more likely than rheumatic disease to cause an eccentric leaflet deformity.

Figure 8

Rheumatic aortic valvular disease, predominant insufficiency. It was impossible to reach the left ventricle and supravalvular injection only was done. The cusps appear normal, but there is marked regurgitation into the left ventricle due to rheumatic aortic insufficiency.

Subaortic Stenosis

Though less common than the valvular variety, subaortic stenosis will be encountered in any thoroughly studied group of young patients with congenital "aortic stenosis" (8 of 21 proved cases in one reported series.[9]). In this probably congenital anomaly there occurs a fibrous ring or ridge, which partially or completely encircles the left ventricular infundibulum at a point 1 to 3 cm. below the normal aortic valve. Important transinfundibular pressure gradients have been repeatedly demonstrated. The symptoms, prognosis, and indications for surgery are related to the degree of obstruction, which varies considerably from case to case. In general, the clinical manifestations resemble those of congenital valvular stenosis.

The differentiation of subaortic and valvular stenosis has been attempted on the basis of the physical findings and the arterial pulse curve. The murmur is similar in both conditions. The presence of a dicrotic notch in the arterial pulse curve, in combination with evidence of aortic stenosis has been put forth as indicative of subaortic stenosis. That this and

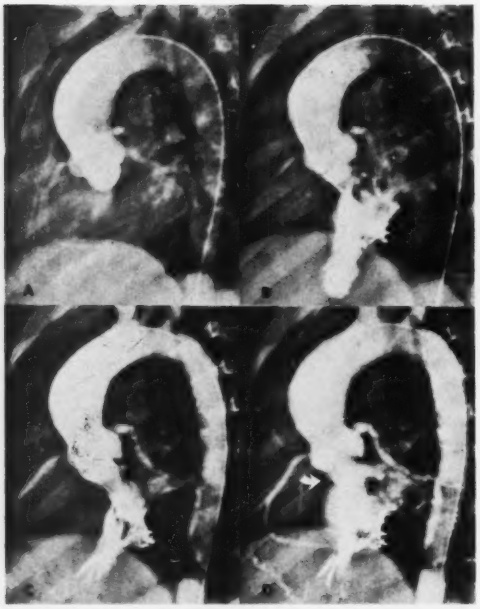

Figure 9

Congenital subaortic stenosis: long-segment infundibular type. A. *Supravalvular injection.* B-D. *Left ventricular sequence. As shown in* A, *the cusps are normal, save for the presence of a small volume regurgitation, which could represent catheter artifact or subclinical insufficiency. Clearly shown on* B-D *(arrow) is an indentation of the left ventricular outflow tract border a short distance below the aortic valve. Pressures found at catheterization: Lower left ventricle, 260/20; aorta, 100/60. Pressures were not obtained in the infravalvular chamber owing to its small size. Following surgical correction of a fibrous ring encircling and deforming the outflow tract, left ventricular and femoral arterial systolic pressures of 125 mm. Hg were recorded. Hypertrophic muscular infundibular outflow tract played no surgically recognized role in this case.*

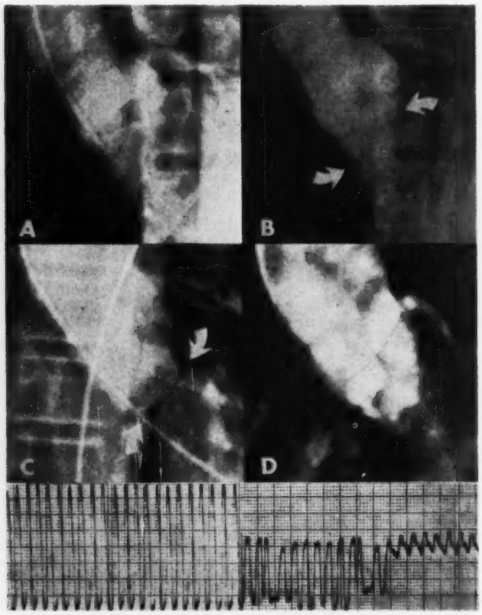

Figure 10

Congenital subaortic stenosis: diaphragm type. A *and* B. *Two different exposures of a subvalvular diaphragm (white arrows) located 3/4 inch below normal aortic valve cusps. As is illustrated here, the finding may be subtle in comparison to the pressure gradients produced. Lesion corrected at surgery. C and D. Subvalvular fibrous ring or diaphragm producing the pressure record illustrated below. Here, outflow chamber pressure was 175/0; the left ventricular subvalvular, 110/0; aortic 110/80.* D *also reveals the presence of minor aortic insufficiency. Open heart surgery confirmed the anticipated presence of a fibrous subvalvular ring.*

the presence of a normal aortic closure sound are quite consistent with severe congenital valvular stenosis may be well explained by the angiographic demonstration of flexibility in the congenital lesion. The large remaining right coronary aortic cusp shown in figure 6 would seem almost incapable of silent closure, despite the eccentric sclerosis and destruction of the other two cusps. The bedside differential diagnosis of subaortic stenosis is not dependable. Conventional fluoroscopy and radiographic examination of the heart is of little value, since the changes are common to both conditions. Calcification in the aortic valves supports valvular stenosis but even here exceptions have been noted.

The recording of blood pressure during the withdrawal of a catheter from the left ventricle to the aorta is a productive approach to the problem. In subaortic stenosis, there is an intermediate zone where ventricular complexes exhibit systolic peaks lower than those of the main ventricular cavity but equal to

those in the aorta. Here, too, artifactual problems abound. In order to minimize catheter recoil and potentially hazardous displacement during forceful contrast injections, the catheters used for this purpose have a number of side orifices near the tip. If these are spread out over too long a segment, the curve may reflect the simultaneous effects of pressures on both sides of a stenotic lesion! Catheter withdrawal must be accomplished at a steady rate and in such a manner as to minimize the curve-corrupting effects of ventricular irritation. Side-holes in the catheter should be closely grouped near the tip. Pure chance appears to play a major role in any event.

Radiologic demonstration of subaortic stenosis requires the injection of contrast agent into the left ventricle. When present in its classical form (figs. 9 and 10), the subvalvular ring is represented by narrow, triangular, radiolucent indentations in the opposing margins of the otherwise tubular left ventricular infundibulum. Because of anatomic variations or projectional factors, this defect is likely to be visualized incompletely. The suprastenotic portion of the left ventricle has not appeared dilated in any of our patients. Although the lesion of subaortic stenosis may create seemingly minor changes on left ventriculography, pressure gradients may be major (fig. 10). The collective data obtained from both radiographic and pressure studies have thus far proved diagnostically sufficient.

Supravalvular Aortic Stenosis

Though a rarity, recent reports and our own experience suggest that congenital supravalvular stenosis of the aorta occurs more frequently than has been supposed. In this condition, the aortic lumen is narrowed by an inwardly protruding ring or band-like obstruction situated just above the aortic valve or 1 or 2 cm. distally, closely related to the point of origin of the coronary arteries. The ring is composed of dense, hyalinized collagen. Anomalies of the aortic valve are commonly encountered in association with the lesion. Bands from the free edges of the

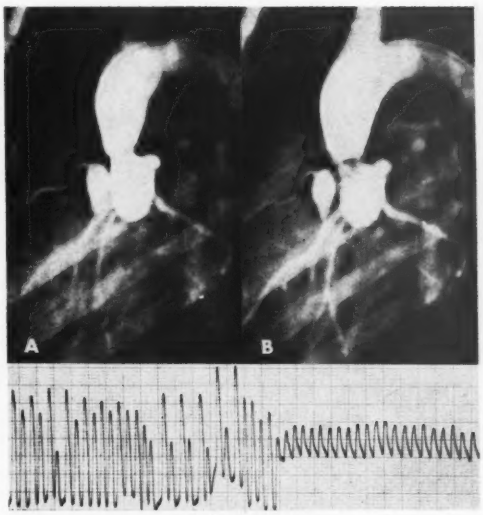

Figure 11

Supravalvular aortic stenosis, congenital: associated valvular involvement. Two views following supravalvular injection reveal the characteristic ring-like constriction of the aorta at the level of coronary artery origin. There appears to be a connection between this and at least one of the aortic cusps. The pull-out pressure record (below) shows a marked ventriculo-aortic systolic gradient but no recognizable supravalvular chamber (due to the small size and aortic leaflet involvement).

cusps to the aortic wall occur, as well as insufficient and bicuspid aortic valves.

That the anomaly is hemodynamically significant is evident from its appearance as well as the fact that young patients predominate in reported autopsy-proved instances. The effects of left ventricular obstruction are reflected in cardiac enlargement and congestive heart failure. Significant trans-stenotic gradients exist. Angina has been a symptom, but syncope has not thus far.

Though one reported patient is said to have had "no significant murmur," a systolic murmur that decreases in intensity with quiet inspiration is characteristic in our experience. It is difficult or impossible to distinguish this lesion from congenital aortic valvular stenosis by conventional diagnostic means. The aortic valve closure sound should be normally audible and normal or reversed splitting of the second sound is possible. An associated

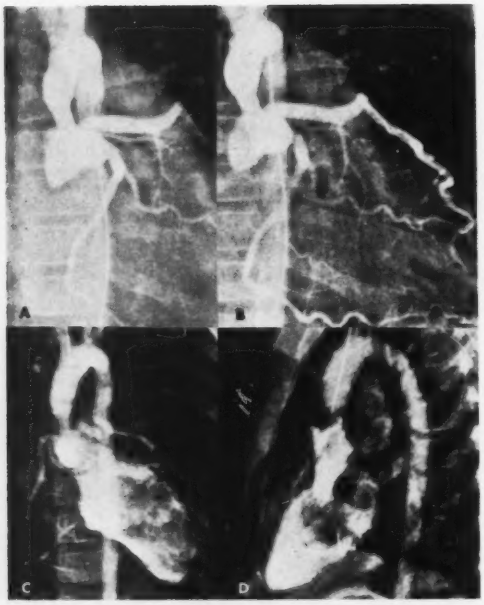

Figure 12

Supravalvular aortic stenosis, congenital: no valvular involvement. A *and* B. *A supravalvular constriction is associated with marked enlargement of the left ventricle and hypertrophy of the coronary system. There is hypoplasia of the aorta distal to the site narrowing. Despite a mechanically satisfactory operative procedure, the patient failed to survive surgery, presumably because of left ventricular insufficiency. Had the lesion been picked up sooner, the result might have been different.* C *and* D. *Case reported in detail elsewhere.*[10] *Frontal and lateral films with injection into the left ventricle disclose a pronounced constriction of the ascending aorta at the level of coronary artery origin. Catheter side-holes made impossible the manometric identification of the supravalvular chamber. Pressures recorded at time of surgery were left ventricular 165/10; aortic 100/50. The surgical procedure was planned on the basis of the films and consisted of an incision carried through the constriction down into the noncoronary sinus. The vertical incision was closed with an oval patch of Ivalon restoring approximately normal aortic caliber. Postoperative result has been considered excellent.*

murmur of aortic insufficiency may denote that one or more aortic cusps are involved in the deformity. Conventional roentgenologic examination has revealed left ventricular enlargement and the changes of congestive heart failure, but usually does not show aortic dilatation. Though the lesion can be corrected by surgery in certain patients, open-heart procedures are required. In addition, the problem of attachment of aortic valve cusps to the ring-stenosis and the relation of the latter to the coronary orifices provide added technical problems. The foregoing make mandatory the use of trans-stenotic catheter studies in the preoperative evaluation of patients with congenital aortic stenosis. Such studies are fortunately definitive in supravalvular aortic stenosis.

Since the lesion exists at a supraventricular level, manometry is not likely to be complicated by the multiple ectopic beats so often associated with the pull-out pressure records in valvular or subvalvular disease. The shorter the supravalvular pocket, the more important it is that the catheter side-holes be confined to its distal portion. In our three cases of supravalvular aortic stenosis, the constriction was sufficiently far above the level of the valve to permit the recording of the pathognomonic pressure curves. In this condition, three distinct pressure zones exist. High ventricular systolic pressure is accompanied by similarly high but otherwise unremarkable proximal aortic pressures although aortic insufficiency may result in abnormally low aortic diastolic pressures. Distal to the stenosis, the systolic level falls abruptly, diastolic pressure being relatively unchanged. It would be difficult to distinguish between the pressure tracings of coaretation of the aorta and the ideal pull-out record of supravalvular stenosis were the catheter positions not known. The important clinical, physiologic, and therapeutic differences between these two conditions are primarily a matter of their location.

Supravalvular aortic stenosis, in the three cases we have observed, has appeared as an unmistakable, bizarre, symmetrical constriction of the aortic lumen at about the level of origin of the coronary arteries, i.e., approximately 1 inch above the aortic valve ring. Although in one of our cases the lesion was shown by conventional angiocardiography, the

superiority of selective injection was unequivocally established when this technic was carried out in the same patient. In one case (fig. 11) a band-like connection was shown between the site of stenosis and the aortic valve. Surgery in this patient has been deferred in the absence of evident left heart embarrassment. That it will be necessary in a few years' time seems likely. Angiographic visualization is of aid, not only in establishing the anatomic diagnosis, but in planning the operative repair. After considerable study of the films reproduced in figures 12C and D, a vertical incision through the aortic wall into the noncoronary sinus and transecting the stenotic zone was made and closed with an oval Ivalon patch with excellent results.[10] A similar surgical procedure was accomplished in another patient (figs. 12A and B), but he did not survive.

Hypertrophic Muscular Obstruction of the Left Ventricular Infundibulum

This curious syndrome, also known as familial muscular subaortic stenosis, has been recognized only recently. In rare patients, the left ventricle hypertrophies so as to create an intrinsic obstruction to its own outflow. Important, and occasionally very large, pressure gradients have been recorded, the transition between high and low pressure regions being found in the subaortic region. Brock[11] has described such an occurrence resulting from systemic hypertension and regards it as an inoperable form of stenosis. Subsequently, others demonstrated a familial incidence of the lesion but cast no light on the cause of the marked cardiac hypertrophy that was found (since systemic hypertension was not present). In the familial form, deaths have occurred in young adulthood. Evidently in some patients with aortic valvular stenosis, resultant subaortic muscular hypertrophy may progress to the point at which an actual impediment to left ventricular ejection is created. Such a condition has its analog in right ventricular infundibular hypertrophy. Muscular subvalvular stenosis associated with valvular aortic stenosis regressed following aortic valvulotomy in a patient reported by Morrow and Braunwald.[12]

Figure 13

Hypertrophic muscular infundibular stenosis of the left ventricle. Two views made during catheter injection into the left ventricle disclose a curved defect and posterior displacement of the outflow tract of the left ventricle. The catheter recorded a pronounced gradient across the infundibulum. There is in addition to the foregoing, a bimarginal indentation in the outflow tract approximately 2.5 cm. below the level of normal aortic valve. Surgery was not attempted and this patient died within 6 months of progressive left heart failure. Autopsy disclosed an unimpressive subvalvular connective tissue ring and considerable hypertrophic enlargement of the intraventricular septum. The latter is believed to have been responsible for the pronounced pressure gradient that was encountered at left heart catheterization. It is possible that the infundibular hypertrophy occurred as a result of the subaortic ring. Catheterization pressure record (below) *reveals a systolic gradient in the outflow tract.*

Diagnosis is simplified when the disease exists in its familial form. An ejection murmur may be heard along the left sternal border and at the apex better than in the aortic area, a finding that does not exclude aortic valvular stenosis. To our knowledge, poststenotic dilatation has not occurred in re-

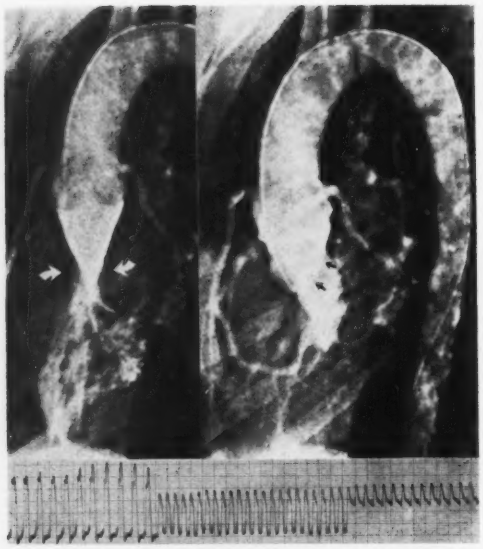

Figure 14

Infundibular obstruction of left ventricle: congenital subaortic ring and associated or secondary hypertrophic muscular obstruction. A-D. *Two views showing a discrete conical subvalvular outflow tract chamber. While the appearance of the outflow tract suggests muscular hypertrophy of the interventricular septum, the well-defined subvalvular chamber in which the catheter lodged repeatedly probably is due to a fibrous subvalvular ring, i.e., subaortic stenosis. Since the patient has not yet been operated upon, it cannot be determined whether hypertrophy is significant and, if so, whether it is primary or secondary in etiology. Pressures obtained at catheterization (illustrated) were left ventricle, 145/5; subvalvular chamber, 100/5; aorta 100/72.*

sponse to muscular obstruction of left ventricular outflow tract. Insofar as the direct approach is concerned, this lesion is not generally considered to be surgically correctible.

In two cases we have studied (figs. 13 and 14), there was left infundibular stenosis and radiologic evidence of enlargement of the interventricular septum. Unlike the more familiar process in the right ventricle, the filling defect seemed to reflect enlargement of the upper half or two thirds of the interventricular septum. The diagnosis of intrinsic muscular infundibular obstruction of the left ventricle by means of left ventriculography should not be accepted unless the "abnormal" radiographic findings are supported by the demonstration of a pressure gradient. Systolic contraction of the normal or ordinarily hypertrophied left ventricle can simulate the finding.

Conclusions

Competent differential diagnosis of the lesion responsible for occlusion of the outflow tract of the left ventricle requires that maximum advantage be made of the specialized technics afforded by left heart catheterization. If, in the course of study of patients with evident aortic stenosis, left ventricular and aortic pressure determination and contrast visualization are routinely carried out, it will be possible to select patients for surgery wisely. By providing precise anatomic information about the location, cause, and abnormal anatomy of the individual obstruction, selective left heart contrast visualization has assumed a critical diagnostic role. Fortunately, it may be accomplished by a safe, reasonably simple percutaneous procedure, which also permits the study of important transstenotic pressure gradients. It is hoped that through further information gained from such technics, the over-all spectrum of obstruction of the left heart outflow tract will be resolved and clarified well beyond the extent achieved in this report.

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Sir Thomas Browne
1605–1682

Sir Thomas Browne, one of the most illustrious medical philosophers, attended Oxford, studied medicine and practiced for 45 years in Norwich where he led a quiet, uneventful life. He had traveled widely on the continent and is said to have received his M.D. degree at the University of Leyden. His eldest son, Edward, became president of the Royal College of Physicians. The fame of Sir Thomas Browne rests almost entirely on four works: *Religio Medici, Pseudodoxia Epidemica,* a discourse on many errors; *Urne-Buriall,* a discourse of the sepulchral urns lately found in Norfolk; *The Garden of Cyprus,* the network plantations of the ancients.

In 1642 a copy of his *Religio Medici,* which he described as "a private exercise directed to myself" was printed from one of his manuscripts and became popular with remarkable rapidity. His erudition, his speculations on the problems of existence, and the quaintness of his style have sustained the appeal of his writings over the intervening centuries. A total of over 55 editions has been published in English, French, Dutch, and German. "I love," he says, "to lose myself in a mystery, to pursue my reason to an O, Altitudo." Interested in natural history, archeology, literature, and theology and blessed by a wide circle of scientific friends, his reflections reached into innumerable areas of inquiry.

In 1664 he was made an honorary Fellow of the Royal College of Physicians and in 1671 he was knighted by Charles II. As Osler remarks, "A life placid, uneventful and easy, without stress or strain, happy in his friends, his family and his work, he expressed in it that harmony of the inner and of the outer man which it is the aim of all true philosophy to attain, and which he inculcated so nobly and in such noble words in the *Religio Medici* and in the *Christian Morals.*"

The end came unexpectedly in his 77th year on his birthday, October 19, 1682.

Unipolar QS Morphology and Purkinje Potential of the Free Left Ventricular Wall

The Concept of Electrical Endocardium

By Demetrio Sodi-Pallares, M.D., Gustavo A. Medrano, M.D., Alfredo De Micheli, M.D., Mario R. Testelli, M.D., and Abdo Bisteni, M.D.

PREVIOUS STUDIES on ventricular activation have shown a rapid, almost instantaneous activation of subendocardial portions of the free left ventricular wall.[1-3] The percentage of myocardium to undergo instantaneous activation has been a matter of divergence among different groups of investigators. Prinzmetal et al.[1] found that up to 80 per cent of the entire thickness of the ventricular wall may be activated simultaneously. Sodi-Pallares et al.[2] reported a value close to 66 per cent, and Durrer et al.[3] the figure of 40 per cent. On the other hand, another group of investigators[4] failed to confirm rapid activation of the subendocardial musculature.

A new series of experiments was planned in this laboratory to seek an explanation for this variation. The free left ventricular wall was explored more extensively by means of bipolar and unipolar intramural leads in order to ascertain whether the differing results were due to differences in procedure among the various authors. Indeed, it will be seen that the variance of results can be partly explained on this basis.

The Purkinje potentials were also registered to study their relation with the unipolar QS complexes obtained in ventricular portions in which a rapid activation was described.

Material and Method

The experiments were carried out in 16 mongrel dogs with use of the standard technics of this laboratory.[5]

The entire thickness of the free left ventricular wall was systematically explored in its anterior, lateral, and posterior regions by means of two types of electrodes. The first, similar to one previously described,[5] consisted of nine pairs of contiguous bipolar leads with each pair separated by a known distance (varying between 1.2 and 1.9 mm.) and with an interelectrodal distance of 0.3 mm., including the diameter of the wire. Once introduced through the ventricular wall, the electrode was fixed at the endocardial surface so that the first pair of bipolar leads would correspond to the endocardium. The second electrode was made up of two steel needles fastened together and insulated except at the tips. The distance between the tips was 0.3 mm., and the recording points were 40 μ in diameter. This electrode was slowly introduced through the ventricular wall until the resistance of the endocardium was felt. After recordings were obtained, the electrode was carefully withdrawn toward the epicardium, millimeter by millimeter, its withdrawal being guided by length marks in its external coat.

With these electrodes, the entire thickness of the free left ventricular wall was explored by recording a contiguous biopolar lead and one corresponding unipolar lead simultaneously with lead II. Sometimes the latter was recorded simultaneously with a series of unipolar leads. It was thus possible to determine at which depth of the ventricular wall unipolar QS complexes and Purkinje potentials were being recorded.

The standardization was not the same for all the experiments, since this was immaterial for the purpose of this paper, but it was kept constant during each experiment.

A Dual-Beam Du Mont type 322-A cathode-ray oscilloscope and preamplifiers model P-4A were used. Recording was made with a Grass C-4C high-speed camera. Film speeds were 250 mm. per second, and the films were amplified twice before study.

Results

Distribution of Unipolar QS Complexes and Purkinje Potentials (A Potentials) in the Free Left Ventricular Wall

1. Mid anterior region. This region was explored at 54 points in nine dogs. Figure 1

From the Department of Electrocardiography of the Instituto Nacional de Cardiología de México, D. F.

Table 1

Distribution of Unipolar QS Complexes and Purkinje Potentials (A Potentials) in the Free Left Ventricular Wall

Region	No. points	QS complexes %	QS complexes FP	A potentials %	A potentials FP
Midanterior	54	40	5	24	3
Anterolateral (lower third)	44	39	4	20	4
Anterolateral (middle third)	72	43	5	22	3
High lateral	14	50	3	14	1
Posterolateral (middle third)	30	36	6	23	2
Posterior (lower third)	14	50	3	28	1

No. points = total number of points explored in the single regions. % = percentage of points at which QS complexes and Purkinje potentials, respectively, were recorded. FP = farthest points at which QS complexes and Purkinje potentials, respectively, were recorded (in millimeters from the endocardium).

and table 1 show the ventricular morphologies and the Purkinje potentials as well as the depths to which they were recorded in each dog. Unipolar QS patterns were recorded at 23 points (40 per cent) and Purkinje potentials at 13 points (24 per cent). The Purkinje potentials usually preceded ventricular complexes of the QS type except when these complexes were recorded at points rather distant from the endocardium (figs. 1, 6, and 7).

2. Anterolateral region (lower third). This region was explored at 44 points in six dogs. Figure 2 and table 1 show the ventricular morphologies and Purkinje potentials as well as the depths at which they were recorded in this group. QS complexes were recorded at 17 points (39 per cent) and Purkinje potentials at 9 points (20 per cent).

3. Anterolateral regions (middle third). This region was explored at 72 points in 10 dogs and the findings are given in figure 3 and table 1. QS complexes were recorded at 31 points (43 per cent) and Purkinje potentials at 16 points (22 per cent).

4. High lateral region. This region was explored at 14 points in two dogs (fig. 2 and table 1). QS complexes were recorded at 7 points (50 per cent) and Purkinje potentials at 2 points (14 per cent).

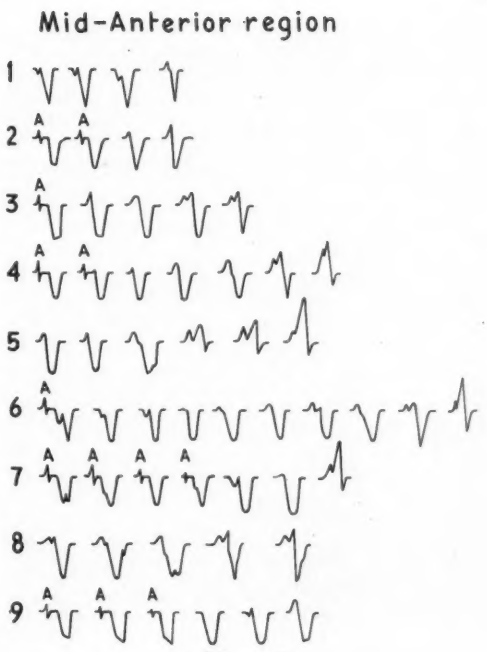

Figure 1

Schematic representation of unipolar intramural complexes obtained by exploring the midanterior region of the free left ventricular wall in nine dogs. In this and in the schemes of figures 2 and 3 the records were made at 1-mm. intervals beginning at the endocardial surface. Purkinje potentials are marked by A.

5. Posterolateral region (middle third). This region was explored at 30 points in three dogs (fig. 3 and table 1). QS complexes were recorded at 11 points (36 per cent) and Purkinje potentials at 7 points (23 per cent).

6. Posterior region (lower third). This region was explored at 14 points in two dogs (fig. 2 and table 1). QS morphologies were at 7 points (50 per cent) and Purkinje potentials at 4 points (28 per cent).

Discussion

Distribution of Unipolar QS Morphologies in the Free Left Ventricular Wall

The distribution of unipolar QS morphologies in the free left ventricular wall of the dog's heart was found to depend upon the

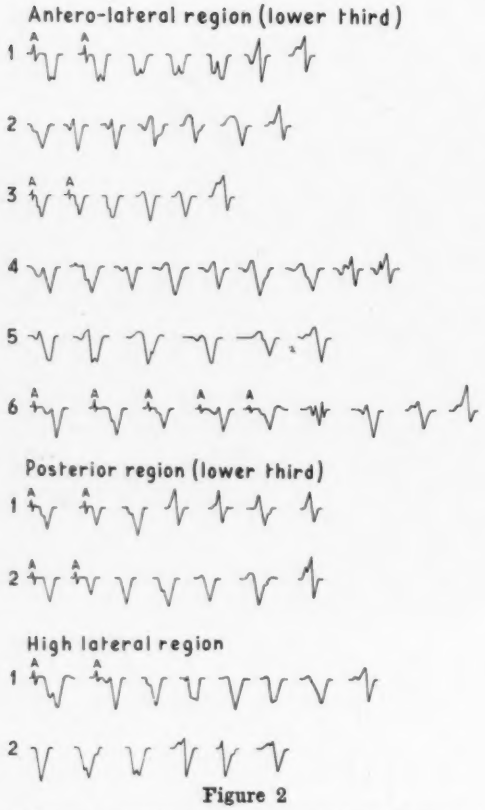

Figure 2

Schematic representation of unipolar intramural patterns obtained in the anterolateral region (lower third) in six dogs, the posterior region (lower third) in two dogs, and the high lateral region in two dogs.

Figure 3

Schematic representation of unipolar intramural complexes obtained in the anterolateral region (middle third) in 10 dogs, and the posterolateral region (middle third) in three dogs.

anatomic region explored and this, in turn, was found to vary from animal to animal. In some regions, such as the midanterior, anterolateral (lower third) and posterolateral (middle third), QS complexes were recorded up to 5 and 6 mm. from the endocardium. On occasion, depending on the thickness of the ventricular wall, QS complexes were found at 2 or 1 mm. from the epicardium.

Figures 4 and 5 are examples of unipolar QS morphologies recorded at varying distances from the endocardium. Figures 6 and 7 show the opposite extreme. No QS complexes are recorded through the whole thickness of the ventricular wall; instead, an initial positivity is inscribed from the endocardial surface.

In general, it can be said that unipolar QS morphologies were found as average in less than 50 per cent of all the points explored (table 1). This, however, is only an average figure, since many individual variations were observed (figs. 1, 2, and 3). On the other hand, this very fact does explain the difference of results reported by the various investigators.[1-3] At present, the previous results can

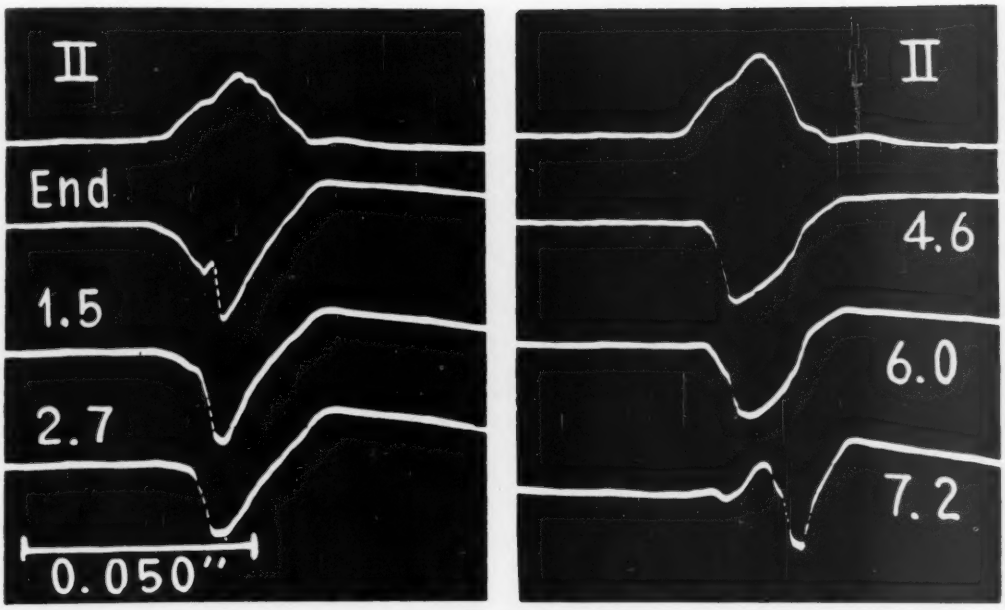

Figure 4

Anterolateral region (middle third). Lead II recorded simultaneously with two sets of three unipolar intramural leads, located from the endocardial surface (End) and to 7.2 mm. away. Unipolar QS complexes are found 6 mm. from the endocardium.

be held as being complementary rather than contradictory.

Distribution of Purkinje Potentials (A Potentials) in the Free Left Ventricular Wall

Purkinje potentials were usually recorded at the endocardial surface and at 1 and 2 mm. from it; in rare instances were they recorded at 3 or 4 mm. from the endocardium (figs. 1, 2, and 3). In some regions, such as the posterolateral (middle third), A potentials were found in all experiments. These potentials were not looked for in basal regions, since it is known from previous experiments[6] that Purkinje potentials are either absent or very scarce there. However, A potentials were recorded at the endocardial surface and at 1 mm. from it in the high lateral region of one dog (fig. 2).

In figure 8, Purkinje potentials are recorded by contiguous bipolar leads (Bm) at the endocardial surface and at 2 and 4 mm. from it. It should be noted that the Purkinje potential precedes to entirely negative morphology (QS) in the corresponding unipolar leads (Un).

In figure 9, Purkinje potentials are recorded at the endocardial surface and at 1.5 mm. from it, both by the bipolar and by one corresponding unipolar lead. At 3 mm. from the endocardium no A potential is registered, while the ventricular complex remains of the QS type in the unipolar lead.

In figure 10, A potentials are recorded by the bipolar lead at the endocardial surface and at 1 and 3 mm. from it. Unipolar QS complexes, however, are obtained up to 9 mm. from the endocardium.

Relationship between Purkinje Potentials and Unipolar QS Morphologies

It has been repeatedly mentioned that, while Purkinje potentials are recorded at the endocardial surface and in subendocardial portions, unipolar QS morphologies are registered at variable depths into the myocardium of the free left ventricular wall (figs. 1, 2, 3, 9, and 10). In our opinion this electrical behavior

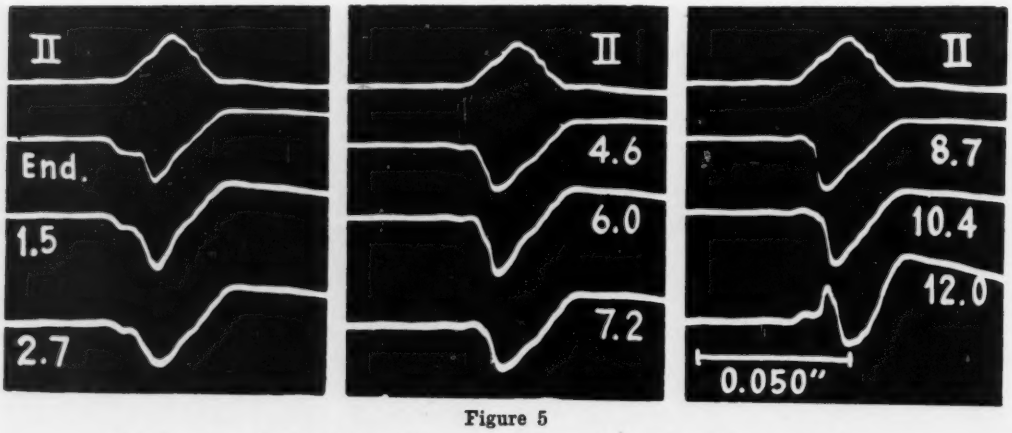

Figure 5

Anterolateral region (middle third). Lead II recorded simultaneously with three sets of three unipolar intramural leads, located at the endocardial surface (End) and up to 12 mm. from it. Only the last unipolar lead obtained at the epicardial surface (12 mm.) shows a significant R wave.

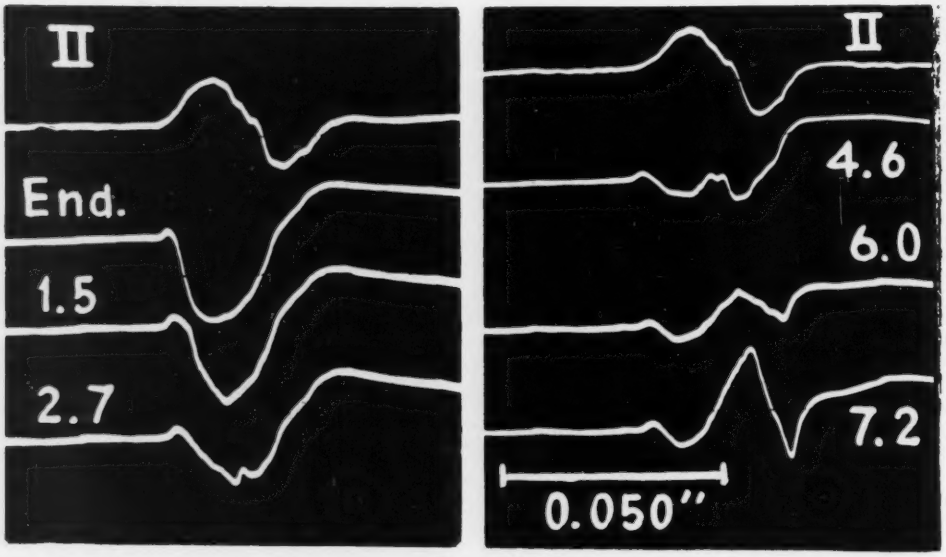

Figure 6

Midanterior region. Lead II recorded simultaneously with two sets of three unipolar intramural leads, located at the endocardial surface (End) and up to 7.2 mm. from it. (Partial right bundle-branch block is present). Initial positivity is recorded at the endocardium (End) and through the entire thickness of the ventricular wall.

is dependent upon the distribution of the Purkinje fibers, as determined by recording the potentials of the specific tissue (A potentials). Also, the variation in distribution of the Purkinje fibers is probably responsible for the individual variations in distribution of the QS complex observed in our series of experiments.

An attempt at summarizing our views on

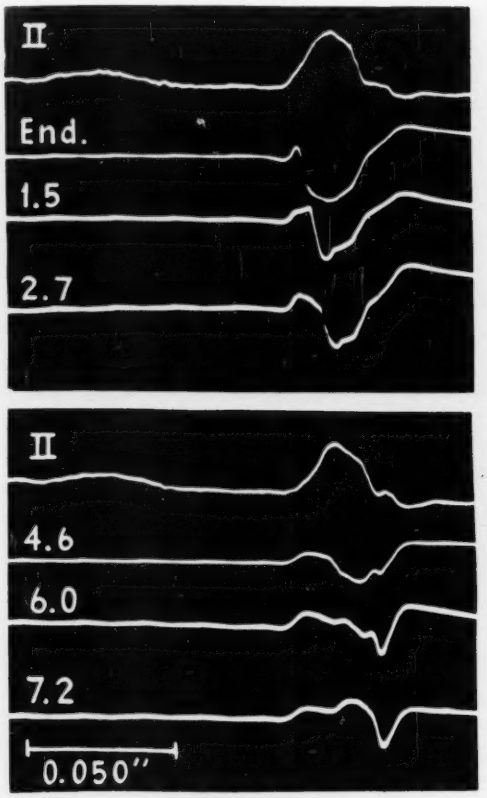

Figure 7

Posterior region (lower third). Lead II recorded simultaneously with two sets of three unipolar leads, located at the endocardial surface (End) and up to 7.2 mm. from it. Compared with figure 6, the initial positivity is more important at comparable points.

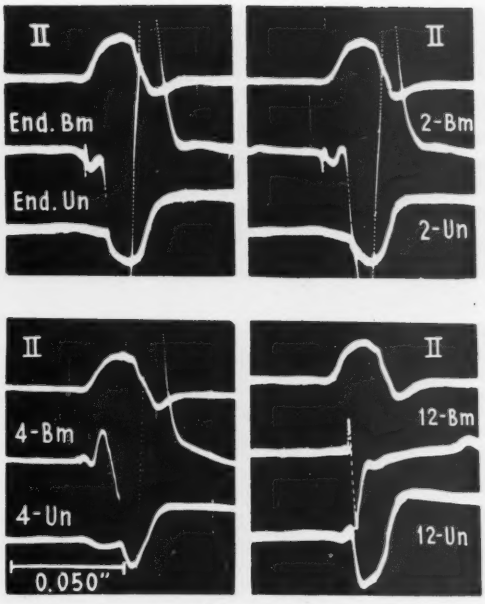

Figure 8

Anterolateral region (lower third). Lead II recorded simultaneously with a contiguous bipolar lead (Bm) and one corresponding unipolar lead (Un) located at the endocardial surface (End) and at 2, 4, and 12 mm. from it. The Purkinje potential, which is seen in the bipolar lead (Bm) up to 4 mm. from the endocardium, precedes to QS morphologies in the unipolar lead (Un).

this matter is made by use of figure 11. In A, a Purkinje fiber extending up to the middle third of the free left ventricular wall is represented before being activated. In B, C, and D, three stages of activation are shown.

After traversing the two bundle branches and their ramifications, the activation arrives at the junction between Purkinje and muscle fibers. In B, the activation front is considered as forming a closed polarized sphere that spreads in all directions, the inside being negative to the outside. For the analysis of the solid angle, the potential at any point outside this sphere is equal to zero, and the potential at any point inside is equal to $-4\pi\phi$.[7] Consequently, an electrode outside the sphere records no electrical activity, while an electrode inside records only negativity (unipolar QS morphology) preceded or not by the Purkinje potential (A), depending on the location of the electrode with respect to the Purkinje fiber. In C, a further stage of ventricular activation is shown. The front of activation still forms a closed polarized sphere, which has reached simultaneously the endocardial surface and an area between the middle and outer thirds of the free left ventricular wall. The potential outside the closed sphere is still zero, and the potential inside remains negative giving rise to negative unipolar morphology (QS). In its successive stages, the closed polarized sphere comes to comprise a series of points which are being activated simultane-

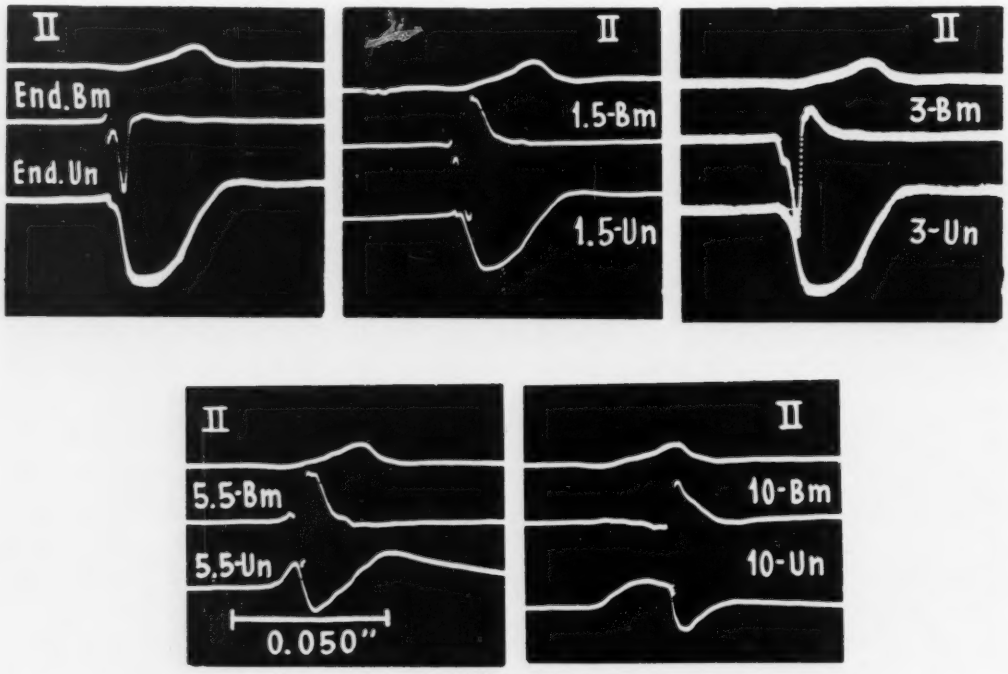

Figure 9

Posterior region (lower third). Lead II recorded simultaneously with a contiguous bipolar lead (Bm) and one corresponding unipolar lead (Un), located at the endocardial surface (End) and up to 10 mm. from it. Purkinje potentials are recorded at the endocardial surface and at 1.5 mm. both by the bipolar (Bm) and the unipolar (Un) lead. QS complexes are recorded by the unipolar lead (Un) up to 3 mm. from the endocardium.

ously, since they are equidistant from the center of the sphere. Then, unipolar as well as contiguous bipolar leads, located at equidistant points inside the closed sphere are synchronous in their recordings. The speed of conduction inside the sphere could be calculated were it possible to orient the exploring electrodes perpendicularly to the activation front, and were it possible to exclude any interference by other spheres of activation, as will be discussed later.

In D, the closed polarized sphere is considered to open to the endocardium. Only now an initial positivity is recorded on the positive side of the activation front, i.e., at points of subepicardial portions not yet activated. It should be noted that just at the moment when the sphere is open to the endocardium, some portions close to the epicardium will be on the negative side of the activation front and in these portions, therefore, unipolar QS morphologies will be recorded.

The foregoing holds true for an isolated Purkinje fiber that extends up to the middle third of the ventricular wall. Assuming that the same Purkinje fiber extended into the middle of the thickness of the ventricular wall, the activation would start at this new location and would reach as a closed polarized sphere both the endocardial and the epicardial surface at the same time. It follows, then, that unipolar QS morphologies would be inscribed through the entire thickness of the free left ventricular wall, and that a unipolar QS recorded at epicardial points would be synchronous with a unipolar QS at endocardial points. These considerations could explain the recording of unipolar QS complexes

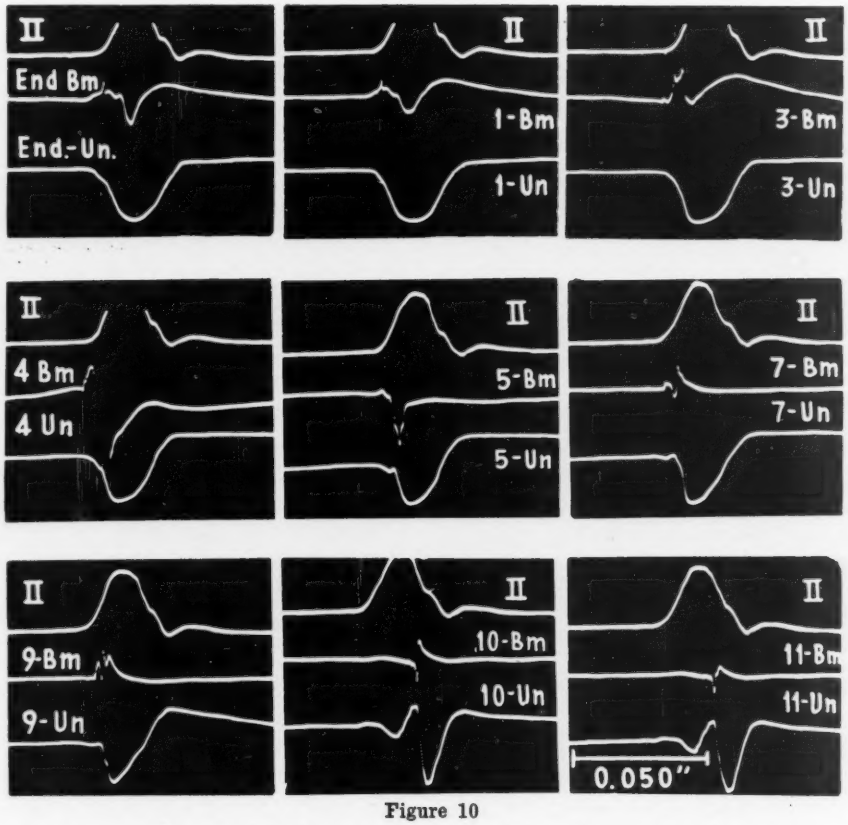

Figure 10

Anterolateral region (middle third). Lead II recorded simultaneously with a contiguous bipolar lead (Bm) and one corresponding unipolar lead (Un), located at the endocardial surface (End) and up to 11 mm. from it. Purkinje potentials are recorded by the bipolar lead (Bm) up to 3 mm. from the endocardium. QS complexes are recorded by the unipolar lead (Un) up to 9 mm. from the endocardium.

at the epicardial surface of the anterior septal projection by Barbato et al.[8]

Taking now into account the totality of Purkinje fibers, the ventricular activation process can be conceived as a number of closed polarized spheres, which independently cause a sequence of simultaneous activated points toward the endocardium and toward the epicardium. Thus, some points in the middle or outer thirds of the free left ventricular wall may be activated before other points close to the endocardium, with the result that the activation process for those points would follow a reverse, i.e., epiendocardial direction, as pointed out by Durrer and van der Tweel.[9] This fact is illustrated in figure 10, where the main deflection, recorded by the bipolar (Bm) at the endocardial surface and at 1 mm. from it, is inscribed later than the same deflection recorded at 3 and up to 9 mm. from the endocardium.

Finally, the sequence of ventricular activation becomes an even more complex phenomenon for two complicating situations, which may be operating at one time. First, closed polarized spheres come to collide among themselves giving rise to one or more closed spheres of larger and irregular contours. Second, spheres of activation open to the endocardium come to interfere with closed spheres result-

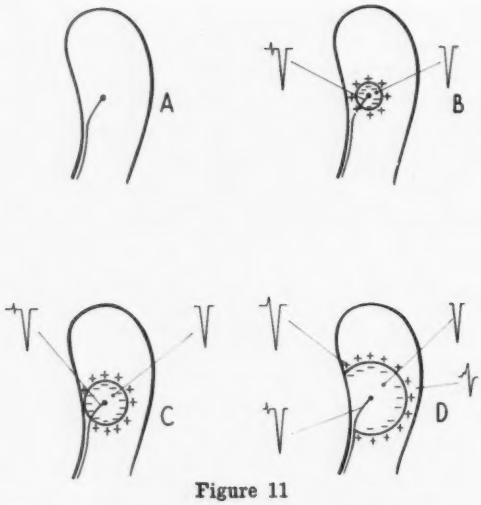

Figure 11

Schematic representation of the activation process of the free left ventricular wall. In A, a Purkinje fiber is represented extending up to the middle third of the ventricular wall. In B, C, and D, three different stages of activation are shown. In B, the activation front forms a closed polarized sphere, the inside being negative to the outside. An electrode outside records no electrical activity (not depicted in the scheme). An electrode inside records unipolar QS morphology, preceded (left of the scheme) or not (right of the scheme) by the Purkinje potential (A). In C, a further stage of ventricular activation is shown. The front of activation still forms a closed polarized sphere. In D, the sphere is shown to open to the endocardium. Only now an initial positivity is recorded on the positive side of the activation front.

ing in complicated spheres open to the endocardium. Thus, at a given moment, a point in the depth of the ventricular myocardium may be considered to have zero potential with reference to a closed polarized sphere not comprising that point. At the same time, however, that point may be considered to have acquired positive potential by the influence of a nearby sphere of activation, which had already opened to the endocardium.

Sequence of Activation and Speed of Conduction through the Free Left Ventricular Wall

It is worth stressing here that the proposed mechanism of closed polarized spheres is invoked to explain the simultaneous activation of subendocardial points and of points at the middle or outer thirds of the left ventricular wall. This type of activation is a consequence of the fact that the depolarization of these portions of the left ventricle is not produced by a single activation front of a simple form spreading in one direction with a uniform rate of conduction, as in the subepicardial musculature. It is rather produced through the combined effects of multiple and independent closed spheres of activation spreading in all directions. It follows, then, that the speed of conduction in ventricular regions with unipolar QS morphologies (electrical endocardium, vide infra) cannot be calculated, since different activation fronts may reach the points that are being explored.

In this connection, it should be mentioned that in these, as well as in any experiments conducted with plunge electrodes, what is actually determined is the sequence of activation at a series of points,[10] that is, the order in which different points become activated by one or several activation fronts.

The Concept of Electrical Endocardium

The electrical endocardium, as referred to the free left ventricular wall, can be defined as an imaginary surface dividing ventricular regions that present unipolar QS morphology, from other regions that present an initial positivity. Only the latter regions contribute to the inscription of the epicardial R wave over the left ventricle.

This dividing surface is dependent upon the degree of penetration of the Purkinje fibers into the myocardium and upon the diameter of the closed polarized spheres before they open to the endocardium. The thickness of the free left ventricular wall does not appear to be as important a factor as the distribution of the Purkinje fibers.

The electrical endocardium can be visualized as a highly irregular surface, which happens to be more or less close to the anatomic endocardium in relation to the factors mentioned earlier. In some regions the electrical endocardium coincides with the anatomic, whereas in other regions of the free ventricular wall it corresponds to portions

close to the epicardium. It would appear, for instance, that the electrical endocardium would be absent in basal portions of the free left ventricular wall, where the Purkinje fibers are also absent or very scarce.[6]

In general, the electrical endocardium can be thought of as an irregular boundary between the inner and middle thirds of the free left ventricular wall (table 1).

In a recent paper on the localization of the dead zone of myocardial infarctions in men,[11] the electrical endocardium was arbitrarily localized at the middle of the thickness of the free left ventricular wall. This correlated well with the findings at autopsy, since any subendocardial infarction that did not extend beyond the middle of the left ventricular wall did not show abnormal Q waves. On the other hand, myocardial infarctions that did extend beyond the middle of the free ventricular wall were so diagnosed for deep and wide Q waves in the 12-lead electrocardiogram.

Summary and Conclusions

The entire thickness of the free left ventricular wall was systematically explored in 16 dogs by means of bipolar and unipolar intramural leads.

The distribution of unipolar QS morphologies was found to depend upon the anatomic region explored and this, in turn, to vary from animal to animal.

Unipolar QS complexes were recorded in less than 50 per cent of all the points explored.

Purkinje potentials were usually recorded at the endocardial surface and at 1 and 2 mm. from it.

The distribution of Purkinje potentials is considered the main factor for the registration of unipolar QS morphologies at variable depths into the myocardium of the left ventricular wall.

The activation process of the free left ventricular wall is conceived to start at the junction between Purkinje and muscle fibers by a number of closed polarized spheres, which independently cause a sequence of simultaneously activated points toward the endocardium and toward the epicardium. In the course of ventricular activation, closed polarized spheres may collide among themselves and may interfere with spheres of activation open to the endocardium.

The speed of conduction in ventricular regions with unipolar QS morphologies cannot be calculated, since different activation fronts may reach the points that are being explored.

The concept of electrical endocardium for the free left ventricular wave is presented.

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In 1719, Alexander Pope the poet moved from Chiswick, and bought a house and five acres of land at Twickenham. He was one of the few at that time who wrote against cruelty to animals and the prevalent passion for brutal amusements. He was now a near neighbour to Hales of Teddington, and, though Pope was a Roman Catholic and had a horror of Hale's experiments, they became friends. Visits to each other's houses were frequent; Pope appealing for expert advice on some horticultural problem, and Hales assisting in laying out Pope's grotto garden. "I shall be very glad to see Dr. Hales," he is reputed to have said, "and always love to see him, he is so worthy and good a man. Yes, he is a very good man, only I'm sorry he has his hands so much imbued in blood." "What, he cuts up rats?" inquired Spence. "Ay! and dogs, too. Indeed, he commits most of these barbarities with the thought of being of use to man. But how do we know that we have a right to kill creatures that we are so little above as dogs, for our curiosity?"—JOSEPH SPENCE. *Anecdotes, observations and characters of books and men, collected from the conversation of Mr. Pope.* London, 1820, p. 293.

Serum Cholesterol and Atherosclerosis in Man

By K. S. Mathur, M.D., F.R.C.P., N. L. Patney, M.D., V. Kumar, M.D., and R. D. Sharma, M.Sc.

HUMAN atherosclerosis has frequently been shown to be associated with derangement of some of the serum lipids. They may well have a bearing on the progression of the atherosclerotic process in man, but to establish this relationship is difficult.

Extensive work has been done on blood cholesterol level in clinically diagnosed cases of atherosclerosis. Cases of myocardial infarction and angina pectoris have been reported to be associated with hypercholesteremia.[1] High serum cholesterol values have been found in persons from a high socioeconomic group who are known to suffer a higher incidence of coronary heart disease.[2] But these studies are of doubtful significance as most of them have been concerned with serum cholesterol levels after, rather than before, myocardial infarction and angina pectoris. Clinical studies alone cannot with certainty establish a correlation between serum cholesterol levels and the extent of atherosclerosis, since the clinical manifestations of atherosclerosis are only the ultimate conflagrations in a long smoldering process. The so-called "normal" population groups also show atherosclerosis at autopsy. The beginning and mild forms of atherosclerosis, which would be of greatest value in studying the possible relationship to concentration of cholesterol in serum, present no symptoms and cannot be diagnosed.

A method more critical than clinical diagnosis is needed to establish a relationship between blood cholesterol concentration and the atherosclerotic process. This is possible by comparing the degree of atherosclerosis seen at autopsy with blood cholesterol levels. The present study was undertaken to correlate the concentration of cholesterol in blood serum with the degree of atherosclerosis seen at autopsy in the aorta and the coronary and cerebral arteries.

From the Cardiovascular Research Unit, Department of Medicine, Sarojini Naidu Medical College, Agra, India.

Material and Methods

Total serum cholesterol estimations were done on samples of blood collected before and after death in 20 unselected cases.

Two hundred cases were then selected for the present study out of 500 consecutive medicolegal autopsies during the period September 1958 to May 1960 at Sarojini Naidu Hospital, Agra. Included in this series are only those cases in which death was sudden, there was no history of recent illness, no evidence of organic disease at autopsy, and the sample of blood was available within 16 hours after death.

The following autopsy material was collected in each case for detailed analysis: aorta, from the valvular ring to its bifurcation; heart with the coronary arteries; brain with the cerebral arteries in situ; and 5 to 10 ml. of blood from the pulmonary trunk or the right side of the heart.

The specimens were carefully washed in tap water and fixed in 10 per cent formalin. The arteries were stained with Sudan IV by the technic of Holman et al.[3] The method recommended by the WHO study group[4] was utilized for the examination of the arteries. The amount and severity of atherosclerosis was assessed by grading and grouping the atherosclerotic lesions and expressing them in a simple formula or atherosclerotic profile, which was further reduced to "an atherosclerotic index" by assigning weights to the factors in the atherosclerotic profile as recommended by Gore and Tejada.[5]

The samples of blood were analyzed the same day for total cholesterol content by the technic of Zak et al.,[6] with use of ferric chloride reagent and slight modification in the preliminary extraction with a chloroform-methanol mixture.

Results

The values of serum cholesterol before and after death in the 20 cases are given in table 1. The period of collection of blood varied from 8 to 36 hours after death.

The total cholesterol in postmortem samples differed significantly from antemortem levels when the blood was collected 16 hours after

Table 1

Serum Total Cholesterol Levels in Twenty Cases

Case no.	Serum total cholesterol in mg. per cent Ante-mortem	Post-mortem	Time of collection of blood after death (hr.)
1	130	105	22
2	100	94	16
3	110	103	16
4	135	137	12
5	150	140	12
6	155	156	14
7	150	144	14
8	175	165	14
9	105	80	24
10	145	115	20
11	155	76	36
12	135	132	12
13	110	100	18
14	145	149	16
15	150	144	15
16	180	172	16
17	145	114	22
18	135	120	18
19	150	116	24
20	122	120	8

death, but the mean difference was not significant when the blood was collected sooner.

The atherosclerotic indices of the aorta and the coronary and cerebral arteries and the mean serum total cholesterol concentration were estimated in all the 200 cases under investigation. These have been analyzed with respect to age in decades (table 2).

The mean atherosclerotic index of the aorta and the coronary and cerebral arteries increased from low values in the early decades to maximal levels in the seventh decade. The mean atherosclerotic indices, i.e., the amount and severity of atherosclerosis in the aorta and the coronary and cerebral arteries, showed progressive increase with age.

The mean serum total cholesterol concentration rose progressively from the first decade to a maximum level in the fifth decade and subsequently declined. The coefficient of correlation was calculated between age and serum cholesterol concentration in each case up to the fifth decade and was found to be 0.19. The value of "t" calculated on the basis of this coefficient of correlation (r) at the 5

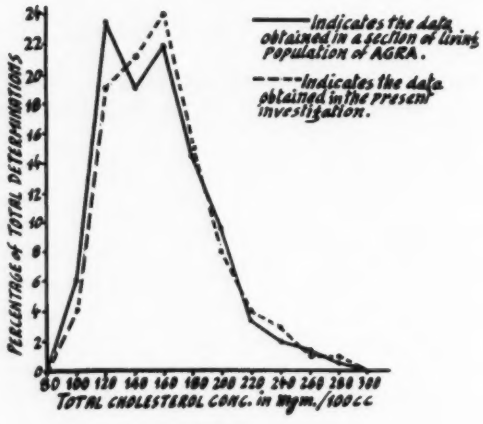
Indicates the data obtained in a section of Urine Population of AGRA.
Indicates the data obtained in the present investigation.
PERCENTAGE of TOTAL DETERMINATIONS
TOTAL CHOLESTEROL CONC. in Mgm./100 cc

Figure 1

Frequency distribution of total cholesterol concentrations.

per cent level was statistically significant and therefore strongly favors the hypothesis that the concentrations of serum total cholesterol are directly related to age, up to the fifth decade.

To compare serum total cholesterol levels with the amount and severity of atherosclerosis in the arteries, all the cases were divided into nine arbitrary groups on the basis of the atherosclerotic index. To facilitate the correlation, the later groups were taken at broader intervals so as to minimize differences in sample size in the groups (table 3).

A continuous rise of mean serum total cholesterol levels for the successive groups of aortic atherosclerosis was observed from the first to the sixth group, but not in the later groups. In the case of coronary and cerebral arteries, there was no correlation.

The correlation of mean aortic atherosclerosis and mean serum total cholesterol may be due to the effect of age or to the pathologic process of atherosclerosis. What follows, is an attempt to dissociate these two processes in their effect on the serum total cholesterol levels.

Effect of age: Despite individual variations, there was definite increase in total cholesterol concentrations of serum for each successive decade up to the fifth. The significance of this

Table 2

Atherosclerotic Indices of Aorta, and Coronary and Cerebral Arteries and Serum Cholesterol Concentrations

Age period (yr.)	Mean age (yr.)	Sample size	Mean atherosclerotic index			Mean serum total cholesterol (mg. %)
			Aorta	Coronary artery	Cerebral artery	
1-10	5	28	0.021 (± 0.198)*	—	—	122 ± 36*
11-20	18	27	0.125 (± 0.05)	0.003 (± 0.04)*	—	141 ± 47
21-30	26	56	0.393 (± 0.28)	0.038 (± 0.05)*	—	158 ± 20
31-40	38	35	1.398 (± 1.17)	0.34 (± 1.48)	0.01 (± 0.25)*	162 ± 32
41-50	46	26	3.02 (± 2.96)	1.47 (± 1.30)	0.29 (± 0.31)	177 ± 38
51-60	56	17	8.95 (± 3.31)	7.44 (± 4.33)	0.43 (± 0.23)	159 ± 40
61-70	66	11	16.13 (± 6.92)	15.71 (± 7.15)	1.04 (± 0.41)	161 ± 20

*Standard deviations.

relationship has been shown previously by statistical analysis.

Effect of atherosclerosis: The mean serum total cholesterol showed a progressive rise from the first to sixth groups of aortic atherosclerosis, but, at the same time, the mean age for each group also increased. Since the amount of atherosclerosis in the aorta increased with age and the serum cholesterol concentration also rose up to the fifth decade, it is important to determine if the significant correlation between the concentration of serum total cholesterol and aortic atherosclerosis is a correlation with severity of atherosclerosis per se or is merely due to the effect of age, or both. In order to determine the significance of the effect of age and atherosclerosis on the serum cholesterol concentration, the coefficient of partial correlation between aortic atherosclerosis and serum cholesterol with age excluded was calculated. No correlation could be found between the two, indicating that, when the age factor was removed, the positive correlation between aortic atherosclerosis and serum total cholesterol is statistically insignificant.

The effect of the severity of aortic atherosclerosis on the serum total cholesterol was tested further by drawing scattergrams in which the aortic atherosclerotic index was plotted against the serum cholesterol level in each case and analyzed by decades. The points were scattered at random, showing that there is no correlation between the serum total cholesterol concentration and the amount and severity of aortic atherosclerosis.

Discussion

Contradictory reports exist on the relationship of blood cholesterol concentration and atherosclerosis,[7-13] but Katz et al.[14] have reported normal values.

No unanimity exists even on the relationship of serum cholesterol to age. The combined evidence, however, points to a rising value of serum cholesterol with age from youth through middle age and to lower levels in older age groups.

Practically no information is available in regard to the validity of total cholesterol determinations in blood obtained post mortem Shope[15] noted the absence of cholesterol esters in blood collected post mortem and concluded that a very active cholesterol-splitting enzyme is present in tissue. Recent evidence indicates, however, that the proportion of combined cholesterol in total cholesterol of serum may be markedly reduced in the presence of infection, and it seems likely that the abnormal

Table 3

Serum Cholesterol Levels and Aortic, Coronary, and Cerebral Atherosclerotic Index

Case no.	Atherosclerotic index	Aorta		Coronary arteries		Cerebral arteries	
		Mean age (yr.)	Mean serum total cholesterol (mg. %)	Mean age (yr.)	Mean serum total cholesterol (mg. %)	Mean age (yr.)	Mean serum total cholesterol (mg. %)
1	No atherosclerosis	6 (11)	125 ± 32*	17 (54)	134 ± 29*	27 (128)	152 ± 41*
2	0 — 0.1	11 (32)	130 ± 45	35 (40)	168 ± 36	43 (18)	175 ± 40
3	0.1— 0.3	17 (35)	149 ± 45	37 (36)	164 ± 37	45 (28)	171 ± 33
4	0.3— 0.5	27 (24)	167 ± 25	48 (18)	167 ± 21	55 (18)	161 ± 21
5	0.5— 1.0	36 (24)	171 ± 16	48 (28)	166 ± 18	55 (4)	159 ± 32
6	1.0— 5.0	45 (23)	175 ± 31	57 (6)	175 ± 24	60 (4)	173 ± 30
7	5.0—10.0	58 (25)	160 ± 39	62 (6)	175 ± 21		
8	10.0—20.0	63 (12)	163 ± 16	60 (4)	190 ± 32		
9	20.0—30.0	61 (14)	162 ± 7	61 (8)	183 ± 26		

The figures in parentheses below mean age indicate the number of cases in the group.
*Standard deviations.

cholesterol picture observed by Shope in the serum was present before death and did not occur post mortem. Certainly it cannot be concluded from Shope's single observation that there is a change in serum cholesterol levels following death. [16, 17]

The frequency distribution (calculated as a percentage) of the concentration of total cholesterol in our selected cases has been compared (fig. 1) with those we obtained in a study of serum cholesterol levels in a comparable group of healthy men of similar economic status and age.[2] Comparison of the two curves offers strong support for our assumption that no significant change in the antemortem level of total cholesterol occurred after death, provided the blood samples were collected within 16 hours after death.

In the present study, the interrelationship between blood cholesterol levels and the amount and severity of atherosclerosis has been evaluated by comparison of blood cholesterol levels with the amount of atherosclerosis seen on direct visual examination of the blood vessel at autopsy.

Our findings of increased serum cholesterol levels from youth through middle age and to lower levels in older persons is in accordance with the results of most workers. The fall of cholesterol levels in old age does not necessarily mean that cholesterol level actually declines. Keys et al.[18] explain this point by stating that the elderly persons with low cholesterol levels were perhaps the survivors of a larger population.

In the present study, we did not find any significant correlation between the blood serum total cholesterol and atherosclerotic index as a representation of the extent and severity of atherosclerosis for any of the vessels studied. The mean serum total cholesterol concentration in the six groups of aortic atherosclerosis showed a successive rise but, when the age factor was taken into consideration, the correlation between atherosclerosis and serum cholesterol in these same groups was found statistically insignificant. In this respect our findings failed to substantiate the findings of Gertler et al.,[9] Morris et al.,[11] and others, who have reported higher values of blood cho-

lesterol with increasing severity of atherosclerosis.

On the other hand, our findings are in accordance with those of Lande and Sperry[16] and Paterson et al.,[19] who determined blood cholesterol levels at intervals during life and compared them with the amount of atherosclerosis found at autopsy. Gofman et al.[20] arrived at similar conclusions.

Iljinski[21] observed high cholesterol levels in cases that showed progressive atherosclerosis with fresh deposits at autopsy but found normal levels in persons with regressive or fibrous modifications of atheromatous changes. Steiner and Domanski[22] found the blood cholesterol of cases with atherosclerosis inconstant and widely fluctuated, whereas values in normal subjects remained relatively constant. Since the normal content of serum cholesterol is close to its saturation point,[22] deposition of cholesterol may follow slight elevations above normal levels, while between times the blood cholesterol levels may be apparently normal.

Summary

Two hundred cases were selected from medicolegal autopsies for a study of the relationship of serum cholesterol to the amount and severity of atherosclerosis in the aorta and the coronary and cerebral arteries. A preliminary study of cholesterol before and after death in 20 cases showed a close parallel between the two when the sample of blood was taken within 16 hours of death.

The mean serum total cholesterol showed a tendency to rise from 122 mg. per cent ±16 in the first decade to 176 mg. per cent ±28 in the fifth decade. A statistically significant correlation was found between serum total cholesterol levels and age up to the fifth decade.

No correlation could be observed between the serum cholesterol level and the amount and severity of atherosclerosis in the arteries. When all the cases were divided into arbitrary groups according to the amount of atherosclerosis, a rise in the levels of mean serum total cholesterol was seen in the first six successive groups of aortic atherosclerosis. But when age was excluded from the correlation between atherosclerosis and serum cholesterol, the interrelationship between the two was found to be statistically insignificant.

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The Spirit of Adventure

Investigators do not march straight to their goal with ease and directness. In their imagination they see a possible fact and they set forth to learn whether their foresight can be realized. Or they come upon something which is puzzling and challenging and which they wish to explain; then they try in various ways to relate it to other phenomena that would solve the riddle. The search for understanding is an adventure or, more commonly, a series of adventures. If an attempt in one direction fails, the failure is not discouraging to an eager explorer. When the goal is reached, there is occasion for joy and exultation. A conquest has been achieved. New knowledge has been gained which deeply satisfies both the explorer's adventurous spirit and his persistent curiosity.—WALTER B. CANNON, M.D., *The Way of An Investigator*. New York, W. W. Norton & Company, Inc., 1945, p. 22.

Electrocardiographic Changes in Head Injuries

By COLIN HERSCH, M.B. (RAND), DIP. MED. (RAND)

THE electrocardiographic pattern of 164 patients with head injury was studied and compared with two control groups: 100 patients with limb trauma and 164 healthy subjects. In the group with the head injury the electrocardiographic findings were correlated with the level of consciousness.

The possible relationship between head trauma and electrocardiographic changes was first suggested by Bramwell.[1] He described a miner, aged 35 years, who, after a blow on the head that did not cause him to lose consciousness, developed atrial fibrillation that lasted for 4 weeks. On examination of the cardiovascular and central nervous systems, nothing abnormal was found.

Lucke[2] described a 54-year-old man who fell from a ladder and was found to have blocked atrial extrasystoles after a period of concussion. His cardiovascular system was clinically normal.

Doret and Forrero[3] studied 32 cases of "traumatic encephalopathy" without clinical evidence of cardiovascular disease. They described various changes but did not find a characteristic electrocardiographic tracing. They divided their cases into six "sympatheticotonic" (tachycardia, raised P waves in leads II and III, short P-R interval, increased Q-T interval, and shallow T waves), four "parasympatheticotonic" (bradycardia, depressed P waves, increased P-R interval, short Q-T interval, and tall T waves), and 22 intermediate types. In addition, one case had ventricular extrasystoles and one case had paroxysmal supraventricular tachycardia. Sinus rhythm was present in 23 cases and sinus arrhythmia in nine.

Nadas et al.[4] described a 5-year-old girl who had a normal pulse 4 weeks prior to a head injury. She was unconscious for 5 minutes and after the injury developed paroxysmal ventricular tachycardia, confirmed by electrocardiography. Her central nervous system and cardiovascular systems were clinically normal, and x-ray examination showed a fracture of the base of the skull.

Electrocardiographic changes have also been noted during brain operations,[5] lumbar puncture[6] and pneumoencephalography,[7] in cerebral tumors,[8] poliomyelitis,[9] and in cerebral hemorrhage.[10]

Much experimental work has been performed to determine the role played by the central nervous system in the production of cardiac irregularities. Beattie, Brow, and Long[11] produced extrasystoles by stimulation of the posterior hypothalamus in anesthetized cats. A destructive lesion of the posterior hypothalamus or section of the brain behind this level caused these extrasystoles to disappear.

Storm van Leeuwen[12] observed nodal and ventricular rhythm, shift of the sinoatrial pacemaker, and multifocal extrasystoles on stimulating the brains of cats between the posterior corpora quadrigemina and the posterior portions of the cerebellum.

Experimental stimulation of subcortical areas in cats by Korteweg et al.[13] yielded the following results: Stimulation of the basal ganglia resulted immediately in occasional extrasystoles. Stimulation of the posterior hypothalamus and the quadrigeminal bodies produced ventricular extrasystoles, wandering pacemaker, and T-wave changes. After stimulation had ceased, ventricular extrasystoles, atrioventricular dissociation, wandering pacemaker, tachycardia, and T-wave changes were noted, all of which were abolished by vagal section.

A study of electrocardiographic changes in head trauma was made by Jacobson and Danufsky[14] in 15 Albino Swiss mice. All the

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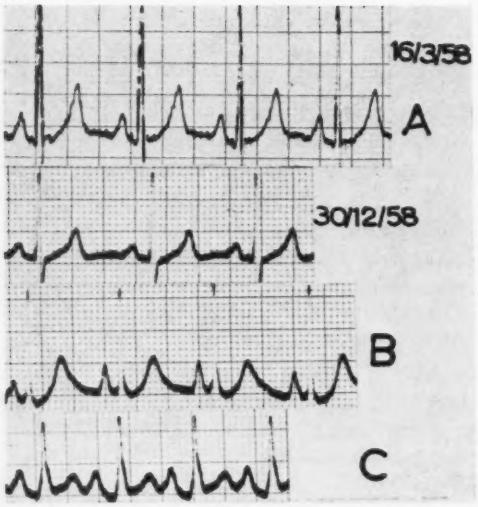

Figure 1

Tall peaked P waves of 4 mm. in height in lead II are seen in A and return to normal 9 months later. B and C, which were recorded from two other patients, also show increased voltage of the P wave in lead II.

mice received intraperitoneal thiopentone prior to the trauma, and six had atropine in addition. Within 20 seconds all nine animals without atropine developed bradycardia, increased amplitude of the T wave, and a variety of arrhythmias—nodal rhythm, sinus arrhythmia, incomplete atrioventricular block, ventricular extrasystoles, and sinoatrial block; in addition, seven of them showed decreased amplitude or inversion of the P wave. In the atropinized group, on the other hand, no bradycardia occurred, one developed T-wave and P-wave changes, and one showed atrial extrasystoles. The authors therefore concluded that the electrocardiographic changes were due to vagal stimulation. At autopsy all the animals had subdural and subarachnoid hemorrhages, a few had cortical lacerations and one had an intracerebral hemorrhage. The brain stems were normal.

In the present paper the effect of craniocerebral trauma on the electrocardiogram has been investigated in Bantu subjects.

Table 1

Changes in Individual Components of Electrocardiogram

	Group A	Group B	Group C
P wave 2.5 mm. or more in S_2	24%	14%	2%
P-R interval more than .22 second	0	0	.6%
QRS complex			
1. Incomplete right bundle-branch block	4%	0	0
2. Complete right bundle-branch block	0	1%	0
3. Voltage S in V_2 + R in V_5*	65% increased Average R + S = 44 mm.	64% increased Average R + S = 43 mm.	48% increased Average R + S = 38 mm.
Q-T_c in seconds†	15% increased .24—.54 (normal .24—.44)	1% increased .29—.44 (normal .29—.43)	All normal (normal .24—.43)
S-T segment raised			3%
more than 2.5 mm. in V leads	14%	19%	
Inverted T waves V_{4-6}	10%	6%	0
U wave more than	21%	21%	.6%
1 mm.	(range 1.2-4 mm.)	(range 1.2-2.5 mm.)	(1.5 mm.)

*Increased voltage: $-SV_2 + RV_5 = >35$ mm.

†Q-T_c measured by the method of Ashman and Hull.[23]

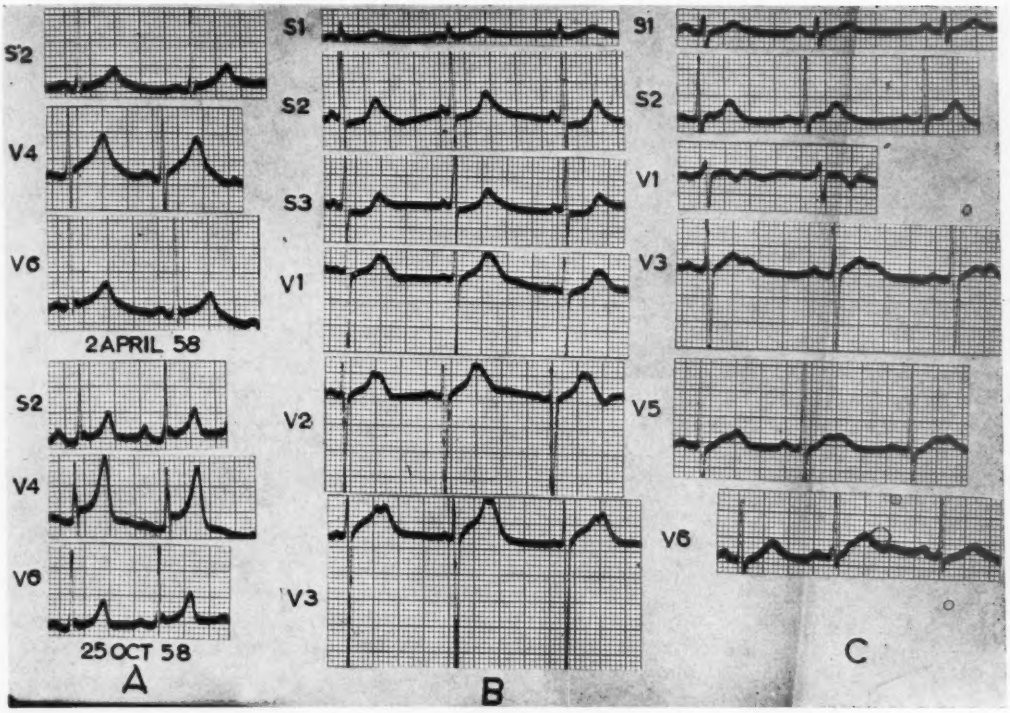

Figure 2

A first shows an increase in the Q-T_c interval. Later the Q-T interval was normal. In tracings from two other patients (B and C) large U waves are present, best seen in V_3.

Table 2

Arrhythmias

	Group A	Group B	Group C
Sinus Arrhythmia			
(a) fixed pacemaker	10%	13%	3%
(b) wandering pacemaker in sinoatrial node	7%	13%	0%
(c) wandering pacemaker to atrioventricular node	3%	1%	0%
Extrasystoles	6%	5%	2%
Nodal rhythm	4%	2%	0%
Atrioventricular block	1%	0%	0%

Table 3

Heart Rates

	Group A 59 Cases	Group B 14 Cases	Group C 4 Cases
Heart rates between 55 and 70 per minute	5	3	0
Heart rates between 70 and 90 per minute	18	4	0
Heart rates above 90 per minute	36	7	4

Subjects and Methods

Three groups of patients were studied. Group A consisted of 164 Bantu patients (158 male and 6 female) with head injury, who were admitted to Baragwanath Hospital over the period March 1957 to March 1958.

There were two control groups: Group B consisted of 100 consecutive Bantu patients who sustained trauma confined to either the upper or lower limbs. These cases comprised fractures, dislocations, traumatic amputations, and bullet wounds. No patients were unconscious or required blood transfusion. Group C was made up of 164 healthy Bantu subjects of age and sex distribution similar to group A.

All the patients in group A were under 40 years of age and all had a history of impaired consciousness. In no case was there clinical evidence of cardiovascular disease. Electrocardiograms were performed within 18 hours of admission to the hospital. The cases were classified into groups according to level of consciousness at the time of the electrocardiograms: group 1 was mentally normal (103 cases), group 2 was drowsy

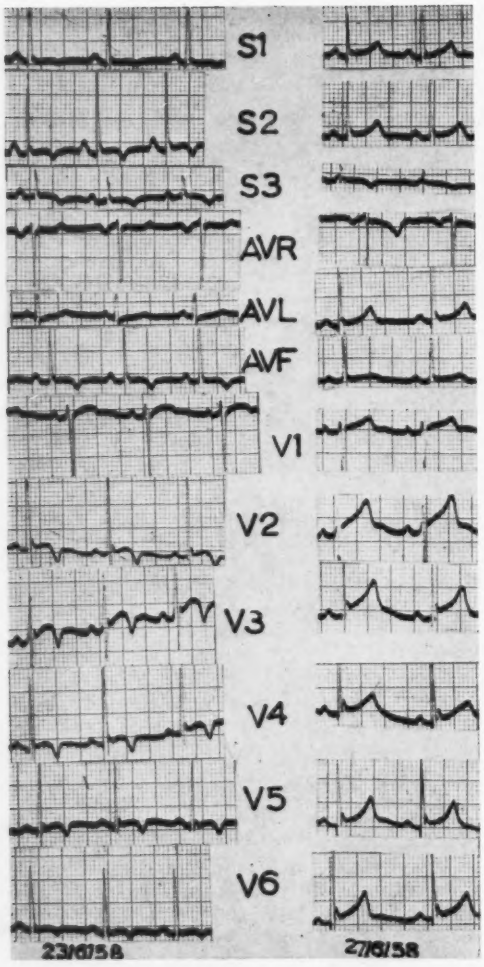

Figure 3

Left. *The T waves were inverted in the three standard leads, aV_F, and V_2 to V_6. Four days later,* right, *T waves became upright except in lead III. The S-T's were elevated in the standard and precordial leads, more marked in the later tracing.*

(12 cases), group 3 was stuporous (29 cases), and group 4 was comatose (20 cases). Eleven patients died, and necropsies were performed in all cases.

Results and Comment

The electrocardiographic findings were divided into the two categories of changes in complexes (table 1) and changes in rhythm (table 2).

The significant findings may be classified as follows:

Changes Occurring More Commonly in the Head Injury Group Than in the Control Groups

P waves of increased amplitude (fig. 1) were found much more commonly in the patients with head injury than in those with limb trauma ($p = <0.05$). In turn, the incidence of tall P waves in the latter group was much higher than that in the healthy controls ($p = <0.05$).

In the head injury group the tall P waves were associated with heart rates above 90 per minute in 61 per cent of cases (table 3). It is possible that these P waves were due to sympathetic stimulation, since similar P waves have been noted during exercise,[15] anxiety,[16] hypoxia,[17] and following the administration of epinephrine.[5] In the remaining cases tall P waves were found with heart rates from 55 to 90 per minute, which suggests that factors other than sympathetic stimulation were operative.

An increased Q-T_c interval was virtually confined to the head injury group, occurring in 15 per cent of the cases (fig. 2A).

The increased Q-T_c interval, like some of the tall P waves, may be due to sympathetic stimulation. In man the injection of epinephrine results in an increase of the Q-T_c interval.[18]

Of the patients with an increased Q-T_c interval, only 36 per cent were accompanied by heart rates of over 90 per minute and 32 per cent also had tall P waves.

Changes That Appeared to Be a Nonspecific Reaction to Trauma

These changes occurred with similar frequency in both the groups with trauma (A and B). At the same time the incidence of the changes in these groups was greater than in the healthy control group C. The p values given below designate the level at which the difference between the traumatic groups and the healthy controls was significant.

1. *Increased QRS voltage in the precordial leads* ($p = 0.02$).

2. *Raised S-T segments (fig. 5) in pre-*

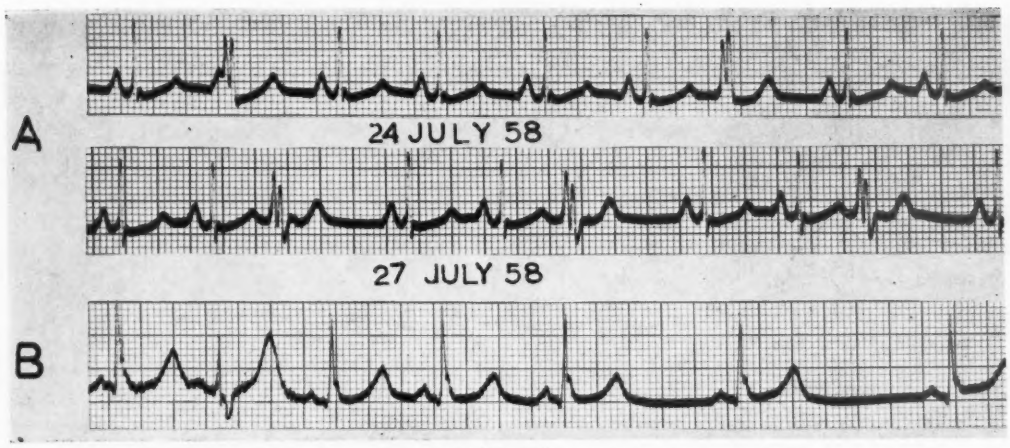

Figure 4

A. *Ventricular ectopic beats were present* (upper) *and later* (center) *the ventricular ectopic beats constituted trigeminal rhythm. Note also the tall P waves.* B. *Shows sinus arrhythmia with a fixed pacemaker and an atrial ectopic beat.*

cordial leads ($p = 0.01$). It is of interest that 48 per cent of the healthy Bantu controls had increased QRS voltage by standards established for white subjects (Sokolow and Lyon[19]). Also, raised S-T segments were found in 3 per cent of such controls. Both increased QRS voltage and raised S-T segments have previously been described by Grusin in normal Bantu.[20]

3. *Inverted T waves in precordial leads* V_1

Table 4

Changes in Individual Electrocardiographic Components

	Group 1 103 Cases	Group 2 12 Cases	Group 3 29 Cases	Group 4 20 Cases
Type of change				
P waves 2.5 mm. or more	23 (22.3%)	3 (25%)	9 (31%)	5 (25%)
Incomplete right bundle-branch block	5 (4.8%)	0	1 (3%)	1 (5%)
Prolonged Q-T_c	16 (15.5%)	0	6 (21%)	4 (20%)
S-T segment raised more than 2.5 mm. in V leads	11 (10.7%)	3 (25%)	4 (14%)	4 (25%)
Inverted T waves V_{4-6}	7 (6.8%)	2 (17%)	3 (10%)	4 (20%)
U waves taller than 1 mm.	11 (10.7%)	1 (17%)	10 (34%)	13 (65%)
Type of arrhythmia				
Sinus Arrhythmia				
(a) fixed pacemaker	7 (6.8%)	3 (25%)	5 (21%)	2 (10%)
(b) pacemaker wandering in sinoatrial node	3 (2.9%)	2 (17%)	3 (10%)	4 (20%)
(c) pacemaker wandering to atrioventricular node	1 (.9%)	1 (8%)	1 (3%)	2 (10%)
Extrasystoles	2 (1.9%)	2 (17%)	1 (3%)	4 (20%)
Nodal rhythm	1 (.9%)	1 (8%)	0	4 (20%)
Atrioventricular block	0	0	0	1 (5%)
Total number of changes	87	18	44	48
Total average number of changes per case	.84	1.50	1.52	2.40

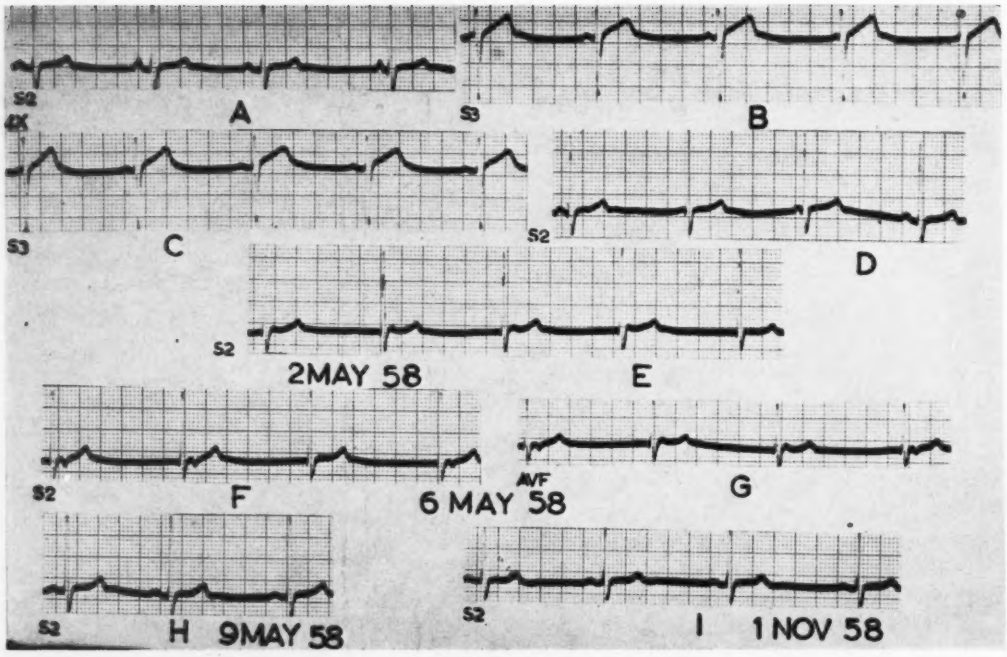

Figure 5

A shows wandering of the pacemaker in the sinoatrial node. In B *the pacemaker wanders to the atrioventricular node. A Valsalva maneuver (x) results in sinus rhythm* (C). *After the Valsalva maneuver,* D *shows wandering of the pacemaker to the atrioventricular node and* E *shows nodal rhythm. Four days later,* F *and* G *show wandering of the pacemaker in the atrioventricular node. Sinus rhythm is restored 3 days later* (H *and* I).

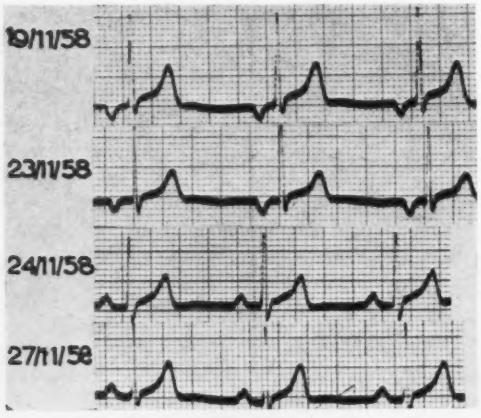

Figure 6

Nodal rhythm reverting to sinus rhythm on the sixth day in lead II.

to V_6 ($p = <0.05$). T-wave inversion in precordial leads V_1 to V_3 may occur normally, therefore only inverted T waves from V_4 to V_6 were considered (fig. 3).

4. *U waves of increased amplitude* ($p = <0.05$). In normal white subjects U waves may be seen in precordial leads in 100 per cent of cases and are usually highest in V_3. Values exceeding 1 mm. are found in only 2 per cent of cases, although values of 2 to 3 mm. may be seen normally. Such waves (fig. 2B and C) are a well-known feature of hypokalemia, but this was found in only one of four cases in which the serum potassium was estimated.

5. *Sinus arrhythmia with fixed pacemaker* ($p = 0.01$). The criteria[22] for this arrhythmia were (1) P-P interval varying by more than 0.16 second, (2) P-R interval of 0.12 second or more, and (3) P waves not varying in shape or direction (fig. 4B).

6. *Sinus arrhythmia with pacemaker wan-*

dering in the sinoatrial node ($p = <0.05$). The criteria for this are similar to those for sinus arrhythmia alone except that the configuration of the P wave varies, depending on whether the pacemaker is in the head, body, or tail of the sinoatrial node[22] (fig. 5A).

All varieties of sinus arrhythmia are generally attributed to vagal stimulation.

Miscellaneous Changes

The remaining electrocardiographic abnormalities were few in number, and detailed statistical analysis was not undertaken. It did appear, however, that ectopic beats (fig. 4A and B) occurred more commonly in the traumatic groups than in the healthy controls. As regards sinus arrhythmia with the pacemaker wandering to the atrioventricular node (fig. 5B, D, F, and G) and nodal rhythm (figs. 5E and 6), there was a suggestion of a decreasing incidence in the three groups—head injury, limb trauma, and normal subjects respectively.

Correlation of the Electrocardiographic Changes with the Level of Consciousness in the Head Injury Group (Table 4)

The number of electrocardiographic abnormalities increased as the level of consciousness deteriorated and all the 11 patients dying from head injuries had marked changes. There was, however, no correlation between the type of electrocardiographic change and the level of consciousness.

Postmortem Findings

In cases that died from head injury it was thought that no useful purpose would be served in attempting to correlate the electrocardiographic changes with the anatomic lesions, since damage to cerebral tissue was invariably gross and extensive. This consisted of combinations of extradural, subdural, subarachnoid, and intracerebral bleeding, edema, and laceration of the brain.

Summary

Electrocardiograms of 164 Bantu patients with head trauma were recorded and studied with reference to two control groups, 100 Bantu patients with trauma to limbs and 164 healthy Bantu subjects.

The electrocardiographic abnormalities that occurred more commonly in the head injury group than in either of the control groups were an increased Q-T_c interval and an increased voltage of the P wave.

Both traumatic groups differed from the healthy controls in showing a higher incidence of increased QRS voltage and raised S-T segments in precordial leads, inverted T waves in precordial leads V_4 to V_6, U waves of more than 1 mm. in height, sinus arrhythmia with fixed pacemaker, and sinus arrhythmia with pacemaker wandering in the sinoatrial node.

The number of electrocardiographic abnormalities increased as the level of consciousness deteriorated.

Acknowledgment

My sincerest thanks are due to Dr. H. C. Seftel, for his advice and help with the manuscript, to Mr. A. M. Shevitz, for the photographs, and to Mr. W. Lutz, for the statistical analyses.

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Harvey's contemporary, Francis Bacon, sagaciously guessed that heat is an expansive motion of particles; but he regarded heat and cold as two contrary principles. Almost in the same generation the brilliant John Mayow perceived a substance in the air "allied to saltpetre," which passed in and out of the blood by the way of the lungs or placenta. "Innate heat" then gave way to phlogiston; but it was not till the discovery of oxygen and of the conservation of energy that we attained a theory of energy, and finally got rid of "matter and form," and of all the thicket of metaphysics, relating thereto; through which in the day of Harvey no mind, however mighty, could have made its way.—THOMAS CLIFFORD ALBUTT, M.A., M.D. *Science and Medieval Thought,* London, C. J. Clay and Sons, 1901, p. 50.

Vectorcardiographic Diagnosis

A Correlation with Autopsy Findings in 167 Cases

By Louis Wolff, M.D., Richard Wolff, M.D., Miltiades D. Samartzis, M.D., Alberto Mazzoleni, M.D., Alvin M. Soffe, M.D., Leopold Reiner, M.D., and Shigeru Matsuoka, M.D.

VECTORCARDIOGRAPHY has been under investigation for a long time, but its application to clinical cardiology is relatively new. For this reason an appraisal of its value as a diagnostic tool is desirable. The limitations of the method have been commented upon, and attitudes have varied from cautious restraint[1, 2] to the prediction that this is the method of the future.[3, 4]

The literature contains only meager autopsy reports, despite their obvious importance, the only sizable series being 50 cases from this laboratory[5] and 59 of Burch et al.[6]

Methods and Material

The present study is concerned with 167 unselected, consecutive cases, that had come to autopsy by December 1958. There were 163 adults, 102 male and 61 female, ranging in age from 31 to 96, and four children, aged 4½, 8, 9, and 12 years.

The instruments, reference system, recording technic, and diagnostic criteria have been described elsewhere.[7–17] The criteria for vectorcardiographic and electrocardiographic diagnosis are given in Appendix I; illustrative cases are in Appendix II.

Left Ventricular Hypertrophy

Criteria for Anatomic Diagnosis

The anatomic diagnosis of left ventricular hypertrophy is based on the weight of the heart and thickness of the left ventricular wall. There is disagreement concerning the upper limits of normal of these two variables.[18] Many factors affect the apparent heart weight and left wall thickness: evaporation of water, amount of epicardial fat, the weight of the other chambers, irregularity of the endocardial surface, dilatation, rigor mortis, and angle of prosector's cut. The criteria, therefore, for the anatomic diagnosis of left ventricular hypertrophy are necessarily arbitrary and subject to error.

Anatomic evidence of left ventricular hypertrophy was considered present when (1) the corrected heart weight was greater than mean plus 3 standard deviations, (2) the corrected heart weight was greater than mean plus 2 standard deviations, if the left ventricular wall was 1.6 cm. or more and the right ventricular wall 0.4 cm. or less, or (3) the corrected heart weight was greater than mean plus 1 standard deviation, if the left ventricular wall was 1.8 cm. or more. The means and standard deviations used for cardiac weight were those of normal people related to sex and body height tabulated by Zeek.[19] Anatomic criteria for left ventricular hypertrophy were fulfilled in 130 of the 167 cases. Nine additional cases, on the basis of strong clinical evidence, almost certainly had left ventricular hypertrophy. They are included in the totals as cases of left ventricular hypertrophy, but are separately indicated in table 1.

Results

Vectorcardiographic signs of left ventricular hypertrophy were present in 106 of the 139 cases with this lesion, a positive correlation of 76 per cent (tables 1, 2, and 3) and in four of the 28 cases in which criteria for anatomic left ventricular hypertrophy were not met. Neither orientation of the initial forces to the left, anteriorly, and inferiorly (table 2), nor myocardial disease (table 3) interfered with the vectorcardiographic diag-

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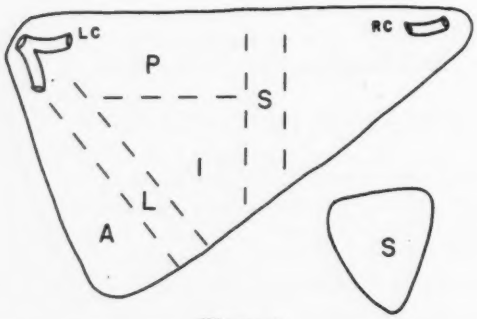

Figure 1

Figures 1, 2, and 3 show the heart unrolled according to the Schlesinger technic. A, anterior wall; L, lateral wall; I, inferior wall; P, high posterior wall; S, septum; LC, left coronary artery; RC, right coronary artery.

nosis. Right ventricular hypertrophy, however, tended to obscure the diagnosis of left ventricular hypertrophy (table 3).

Right Ventricular Hypertrophy

Criteria for Anatomic Diagnosis

Right ventricular enlargement, except when massive, contributes but a minor addition to the total heart weight; therefore, thickness of its wall was the only criterion considered in evaluating right ventricular hypertrophy.

Right ventricular hypertrophy was considered present when the right wall was 0.6 cm. or more and absent when it was 0.3 cm. or less. Right wall thicknesses of 0.4 or 0.5 cm. precluded a definite decision about the presence or absence of right ventricular hypertrophy, and these cases were classified as equivocal.

Anatomic criteria for right ventricular hypertrophy were present in 60 cases, absent in 34, and equivocal in 73.

Results

A vectorcardiographic diagnosis of right ventricular hypertrophy was made in 15 of the 60 cases with this lesion, in none without anatomic right ventricular hypertrophy, and in only one of the 73 cases with equivocal right hypertrophy (table 2). Orientation of the initial forces to the left, anteriorly, and inferiorly (table 2) did not interfere with the vectorcardiographic diagnosis of right chamber enlargement.

Of 55 cases with anatomic left and right ventricular hypertrophy, the vectorcardiogram displayed left ventricular hypertrophy alone in 30, right ventricular hypertrophy alone in 11, biventricular hypertrophy in two, and no hypertrophy in 12.

Myocardial Disease

Anatomic Data

The anatomic data in relation to myocardial disease embrace the presence, location, size, and age of the lesion. Localization was tabu-

Table 1

Summary of Anatomic, Electrocardiographic, and Vectorcardiographic Diagnoses in 167 Patients

Case no.	LVH	RVH	ACP	Myocardial Infarction						RBBB	LBBB	IF LAD
				Any	Ant	Inf	Sep	Lat	H-P			
1	AV	AV	A							E		
2	AVE	A		A		A	a				VE	
3	A E	A								E		
4	AV	A		AV	AV	A	aV	A	a		E	
5	AVE			AVE	AVE	AV		AVE	A			
6	A	A		AVE	AVE	AVE	AVE	AV	A	VE		
7	AVE	A		aV		aV						
8	AV	A		AVE	V	AVE	AVE		A			
9	AVE	A		E	E			E				
10	AVE			A	A	a	a	A	a		VE	
11	AV											
12	A	A		AVE	AVE	A		AVE	AV			
13	AV	A		A		a	a		A		VE	
14	AV			AVE	a E	AV	AVE	a E	aV	VE		

Table 1 (*continued*)

Summary of Anatomic, Electrocardiographic, and Vectorcardiographic Diagnoses in 167 Patients

Case no.	LVH	RVH	ACP	Myocardial Infarction						RBBB	LBBB	IF LAD
				Any	Ant	Inf	Sep	Lat	H-P			
15	AVE			AVE	V	AVE	AV					
16	AV			AVE		AVE	AV					
17	AV			AVE	a	AVE	AV	AV	A			
18	AV	A		AVE		AVE	AV					
19		A										
20	AVE	A		a	a			a			VE	
21	AVE											
22	AVE											
23	A			a		a			a	VE		
24	A	AV								VE		
25	A	A	AV									
26	AVE										VE	
27	AV	A										
28	AVE			AV		AV						
29	AV			A		A		a			VE	
30	A	E	AV									
31	A	AVE										
32	AV			a	a	a	a				VE	
33	AVE			A	A	A	A	a			VE	
34	AVE			AVE	AVE	AV	aVE	a				
35	E	A E										
36	AV	A		AVE	AV	AVE	AV	a				
37	AVE	AVE		a	a	a						
38				AVE	a	AVE	AV	AV				
39	A	A										
40	AVE			A	A	a	a	a				
41	AVE	A		A				a	A			
42	AV	A	A	AVE	A	AVE	AVE	a	A			
43	AV	A		AVE	AVE	AV	AV	AV	a			V
44	AVE			A	A	a	A	a	A			
45	AVE	A		AVE	AVE	AVE	AV	A	A			
46	AV			a	a	a					E	V
47	A	AVE								V		
48												
49	E			a	a			a				
50	AV	A		AVE	E	AV	a VE		A			
51	A E	A		a VE		a VE	a	V				
52	AV	A								VE		
53	AVE			a		a						
54			A									
55	AVE									VE		
56	E			E		E				VE		
57	AVE	A		AVE	AV	AVE	AVE	a V	a			
58	A E	A E										
59	A E	AVE										
60	CV											
61	A	AVE										
62	AVE			AV	AV		a					V
63	A E										VE	
64	AV		A	AV	a V	V	AV	a	A	V	E	
65	A E	AVE								V		
66	A	AV										V
67	CV									VE		

Table 1 (*continued*)

Summary of Anatomic, Electrocardiographic, and Vectorcardiographic Diagnoses in 167 Patients

Case no.	LVH	RVH	ACP	Myocardial Infarction						RBBB	LBBB	IF LAD
				Any	Ant	Inf	Sep	Lat	H-P			
68	A E											
69	AVE			A		a		A				
70	A E			AVE	AVE					VE		
71	AVE			AV	AV							
72	A	AVE								VE		
73	A	A E										
74	AVE			A			A	A			E	V
75	A									VE		V
76	AVE			AV	AV		A	a				
77	AVE											
78	AV			a		a	a					
79	AVE			a VE		a VE	a					
80				a		E	a		a			
81	V			AVE		VE			A			
82	AVE											
83	AV			AVE	AVE	AVE	A	VE				
84	AVE	A		AVE	AVE							
85	AV			AV		V	A	A				
86	AVE			AVE		AVE	A	V				
87	AV	A		AVE	AVE	AVE	AVE	A		VE		
88	AV											
89	AV	A										
90	AV	A		A	A						E	V
91		AVE										
92	A	AVE										V
93	A											V
94	A	AV										V
95	A	AVE										
96	CV											
97	AV	A		AV	AV		AV					
98	AV			AVE	AVE	AVE	AVE	A	A			
99	AVE			AVE	AVE	a	a E	a	a			
100	CV			a	a	a	a	a				
101		AV								V		V
102	AVE			a		a						
103	AVE		A	a VE	a V	a VE	a	a	a			
104				a VE	a	a VE	a V	a E	a V	VE		
105	CV	A		AV		AV						
106	A E	A		a		a		a		VE		
107	AVE	A		a		a	a	a	a		VE	
108	AVE			AVE	a	AVE	AVE	a				
109	AV			AVE	AVE	AVE	a V	AVE	a			
110	AVE											V
111												
112	AV			A				A	A		VE	
113	AVE										VE	
114	AVE			AV		AV	A					
115	AVE										VE	
116	AVE			AV	AV	a	A	a	a		E	V
117	AV										VE	
118	AVE			AVE		AVE	a	A				
119	A E	VE	A							V		V
120	AV											

Table 1 (*continued*)

Summary of Anatomic, Electrocardiographic, and Vectorcardiographic Diagnoses in 167 Patients

Case no.	LVH	RVH	ACP	Myocardial Infarction						RBBB	LBBB	IF LAD
				Any	Ant	Inf	Sep	Lat	H-P			
121	AVE											
122	A											
123	CV		A	A	A	A	A	a			E	V
124	AV			a VE	V	VE	a V					
125										VE		
126				AVE	A E	AVE	A E	a V		VE		
127				AVE	AVE	AV	AV	a	a			
128	AV			AVE	a V	AVE	a V		A			
129											VE	
130											E	V
131	AV			AVE	AVE	AVE	AVE	a	A			
132	V			AV		AV	A	a	A			
133	V		AV									
134	A			AVE	AVE	AVE	AVE	A	A	VE		
135	AVE	A		AVE	AV	a VE	a	a	A			
136	AVE			AV		AV	AV	AV			VE	
137	AV		A	AVE	A	AVE	A E	a V				
138	A E	A									VE	
139	AV		A	AV	AV	A		A	A		E	
140	AVE			a E	E			E	a	VE		
141				a V	a V	a V	a V	a V	a			
142			AVE									
143	CV	A		A		A	A				VE	
144	AVE			a		a	a	a				
145	CV			AVE	AVE			AVE				
146	AVE			a	a	a		a				
147				AVE	AV	a VE	a V	A	A			
148	AVE		A	A	A	a		a				V
149	AVE											
150	AVE			AV		AV	A		A		VE	
151	AVE			AVE	AVE	AVE	AVE	a	a			
152	AVE	A									VE	
153	AV	A										
154	A	A		A			A					
155				A	a	A		A				
156	AV			AV	A	AV	A	a V	a			
157	V			AVE	a	AVE		AVE	A			
158	AVE	A										
159	AV			a		a						
160	AV			VE	VE	V						
161										VE		
162	AV											
163	A E	A		AVE	A E	AVE	AV	AVE	AV	VE		
164	CVE											V
165		A										
166	AVE	A		a				a			VE	
167	E											

Key to abbreviations:

LVH, left ventricular hypertrophy; RBBB, complete or incomplete right bundle-branch block; IF LAD, initial forces directed left, anteriorly, and inferiorly other than LBBB; V, diagnosed from vectorcardiogram; ACP, acute cor pulmonale; RVH, right ventricular hypertrophy; LBBB, complete or incomplete left bundle-branch block; A or a, present anatomically. In cases of infarction A, large; a, small infarct; E, diagnosed from electrocardiogram; C, anatomic criteria not fulfilled but present on clinical grounds.

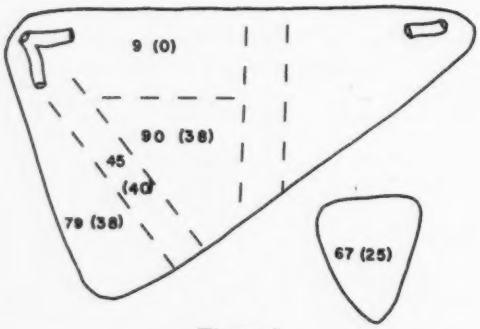

Figure 2

Percentage of cases with large infarcts in which a vectorcardiographic diagnosis of infarct in the various locations was correctly made. Unbracketed numbers refer to cases with initial forces oriented to the right, bracketed numbers refer to cases with initial forces oriented to the left, anteriorly, and inferiorly.

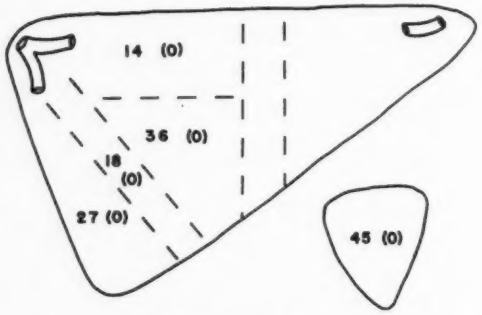

Figure 3

Percentage of cases with small infarcts in which a vectorcardiographic diagnosis of infarct in the various locations was correctly made. Unbracketed numbers refer to cases with initial forces oriented to the right, bracketed numbers refer to cases with initial forces oriented to the left, anteriorly, and inferiorly.

lated in each case on a map of the heart unrolled according to the Schlesinger technic[20] (fig. 1). All lesions less than 1.5 cm. in diameter were classified as small, those 1.5 cm. or greater as large. It was usually possible to determine by careful study of the clinical and autopsy records that a given lesion was or was not present when the vectorcardiogram was obtained. That this is a possible source of error is obvious.

Myocardial disease was found in the left ventricle in 98 cases, large lesions in 73, and only small ones in 25. In the 98 cases, there were 307 areas of infarction: 77 in the inferior wall, 67 in the interventricular septum, 61 in the lateral wall, 59 in the anterior wall, and 43 in the high posterior wall. Five areas were involved in 25 cases, four areas in 19, three in 13, two in 26, and one area in 15.

Results

The initial forces in 21 of the 98 cases with infarction were oriented to the left, anteriorly, and inferiorly; 13 of these were considered instances of left bundle-branch block. The correlation between the vectorcardiographic diagnosis of myocardial disease and

Table 2

Correlation between Vectorcardiographic Diagnosis and Anatomic Hypertrophy

		Hypertrophy present			Hypertrophy absent		Hypertrophy equivocal	
		Autopsy	VCG diagnosed	%	Autopsy	VCG over diagnosed	Autopsy	VCG diagnosed
IF—right	Left ventricular hypertrophy	103	78	76	25	4		
	Right ventricular hypertrophy	46	11	24	24	0	58	0
IF—LAD	Left ventricular hypertrophy	36	28	78	3	0		
	Right ventricular hypertrophy	14	4	29	10	0	15	1
All cases	Left ventricular hypertrophy	139	106	76	28	4		
	Right ventricular hypertrophy	60	15	25	34	0	73	1

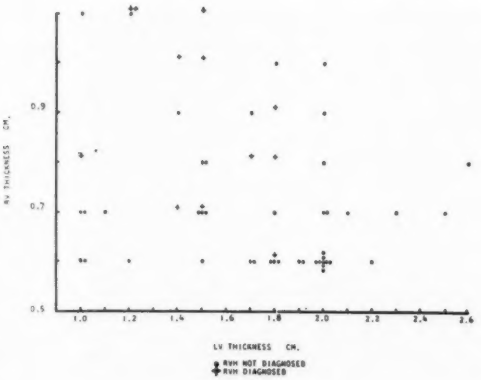

Figure 4

Correlation between diagnosis of right ventricular hypertrophy and left ventricular wall thickness in 56 cases (ventricular wall measurements not available in four cases with gross anatomic hypertrophy).

the anatomic findings is shown in table 4 and figures 2 and 3.

Acute Cor Pulmonale (Pulmonary Embolism)

There were 13 cases in which acute pulmonary embolism was present when the vectorcardiogram was recorded; the diagnostic pattern of acute cor pulmonale was observed in three of these. In a fourteenth case, one with intractable fatal bronchial asthma, the vectorcardiogram disclosed the pattern of acute cor pulmonale. Pulmonary embolism was not found at autopsy, but there were dilatation of the right ventricle and the findings characteristic of acute fatal bronchial asthma.

No Heart Disease

Of the 167 cases, three had pulmonary embolism without heart disease; of these, two were diagnosed as acute cor pulmonale, and in one of them an additional but incorrect electrocardiographic diagnosis of left ventricular hypertrophy was also made. Eight other patients had completely normal hearts; in these the vectorcardiograms were either normal or displayed bundle-branch block.

Discussion

The two major determinants in the result of a pathologic correlation are the criteria used for anatomic diagnosis and the performance of the test under investigation. Regardless of how good the clinical test is, if the criteria for anatomic diagnosis are inadequate, as in right ventricular hypertrophy, the correlation will necessarily be a poor one. The anatomic criteria for left ventricular hypertrophy are considerably better, and the correlation is better. The most reliable postmortem findings are those of myocardial infarction or fibrosis, and the correlation is good. It should be pointed out, however, that studies of this sort are inadequate and misleading unless careful gross and microscopic study of the heart is made.

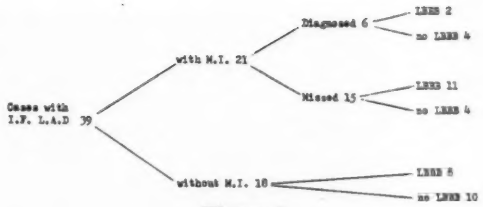

Figure 5

Diagnosis of myocardial infarction in cases with initial forces oriented to the left, anteriorly, and inferiorly divided into those with and without left bundle-branch block. I.F. L.A.D., initial forces oriented left, anteriorly, inferiorly; M.I., myocardial infarction; LBBB, left bundle-branch block.

Ventricular Hypertrophy

Because biologic measurements generally follow a binomial distribution curve with the upper limit of normal overlapping the lower limit of abnormal, the performance of a test depends in part upon the selection of criteria; the higher the incidence of correct positive diagnosis, the greater is the likelihood that false positive diagnoses will be made. Conversely, if criteria are chosen so as to eliminate false positives, the expectation is that fewer correct diagnoses will be made.

It is, therefore, not surprising that with criteria sufficiently rigid to eliminate false-positive diagnosis of right ventricular hypertrophy, the correct diagnosis was made in only 25 per cent of those with right ventricles measuring 0.6 cm. or more in thickness. Even 25 per cent is an overestimate of the performance of the vectorcardiogram, since, doubtless, many cases with right ventricular thick-

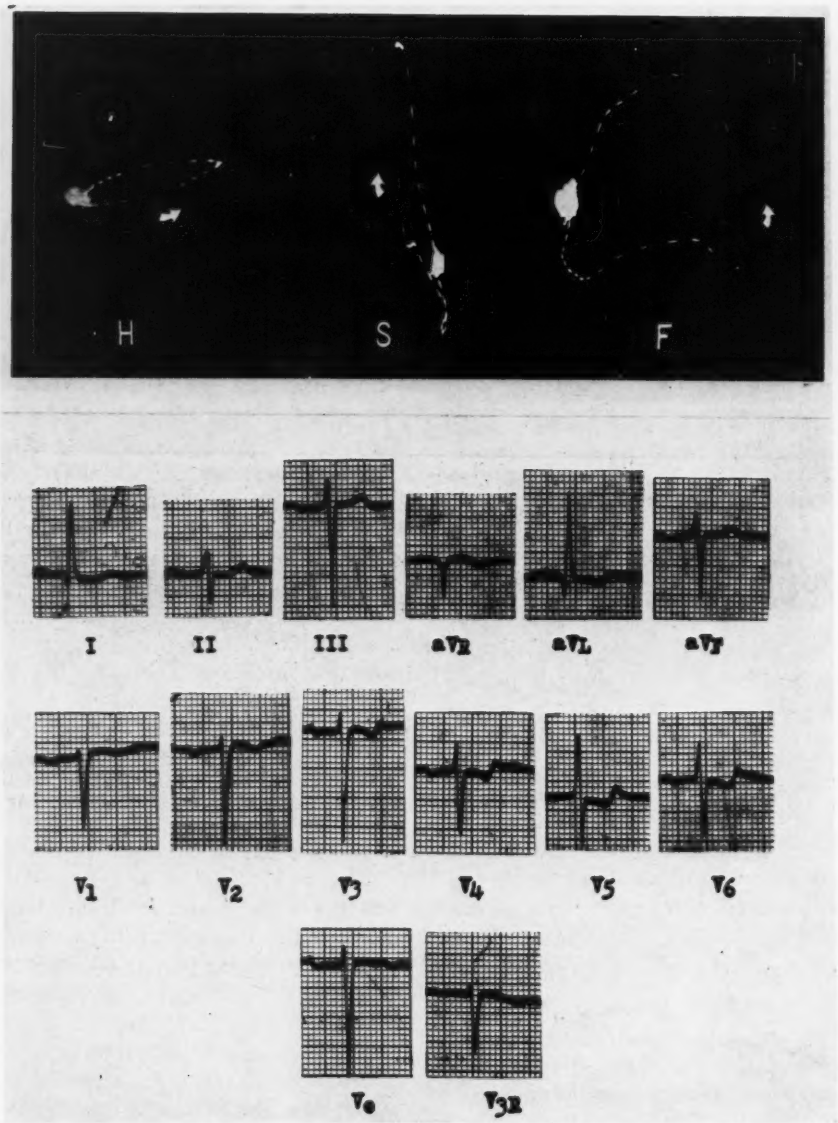

Figure 6

Vectorcardiogram and electrocardiogram in case 76, table 1. Vectorcardiogram interpreted as anterior myocardial infarction and left ventricular hypertrophy, electrocardiogram as left ventricular hypertrophy. Autopsy showed both anterior myocardial infarction and left ventricular hypertrophy.

nesses of 0.4 or 0.5 cm. had right ventricular hypertrophy. The performances of the electrocardiogram (22 per cent) and of the electrocardiogram plus vectorcardiogram (30 per cent) do not differ significantly from this figure. Thus, our data show that a vectorcardiographic diagnosis of right ventricular hypertrophy is reliable evidence of a large

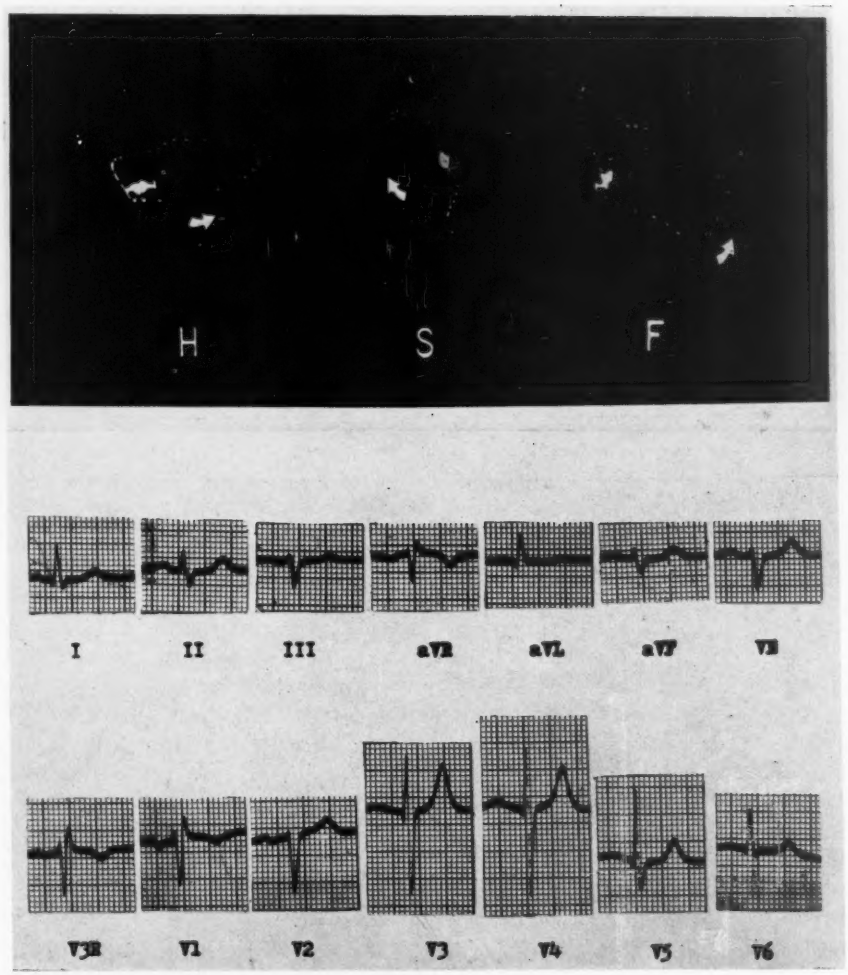

Figure 7

Vectorcardiogram and electrocardiogram in case 162, table 1. A vectorcardiographic diagnosis of left ventricular hypertrophy was made. None of the conventional indices of left ventricular hypertrophy is met in the electrocardiogram, which simulates right bundle-branch block. Autopsy revealed left ventricular hypertrophy.

right ventricle but that the failure of the vectorcardiogram to display the pattern of right ventricular hypertrophy has very little value in ruling out anatomic right ventricular hypertrophy. The possible role of left ventricular hypertrophy in preventing the development of vectorcardiographic signs of right ventricular hypertrophy is difficult to assess in the present study, since only five cases of right ventricular hypertrophy without left ventricular hypertrophy are available for comparison. Figure 4 shows that no diagnosis of right ventricular hypertrophy was made when left ventricular thickness exceeded 1.8 cm. It appears likely, therefore, that concomitant left ventricular hypertrophy does in fact obscure the diagnostic signs of right ventricular hypertrophy.

In the case of left ventricular hypertrophy, the criteria selected take account of the over-

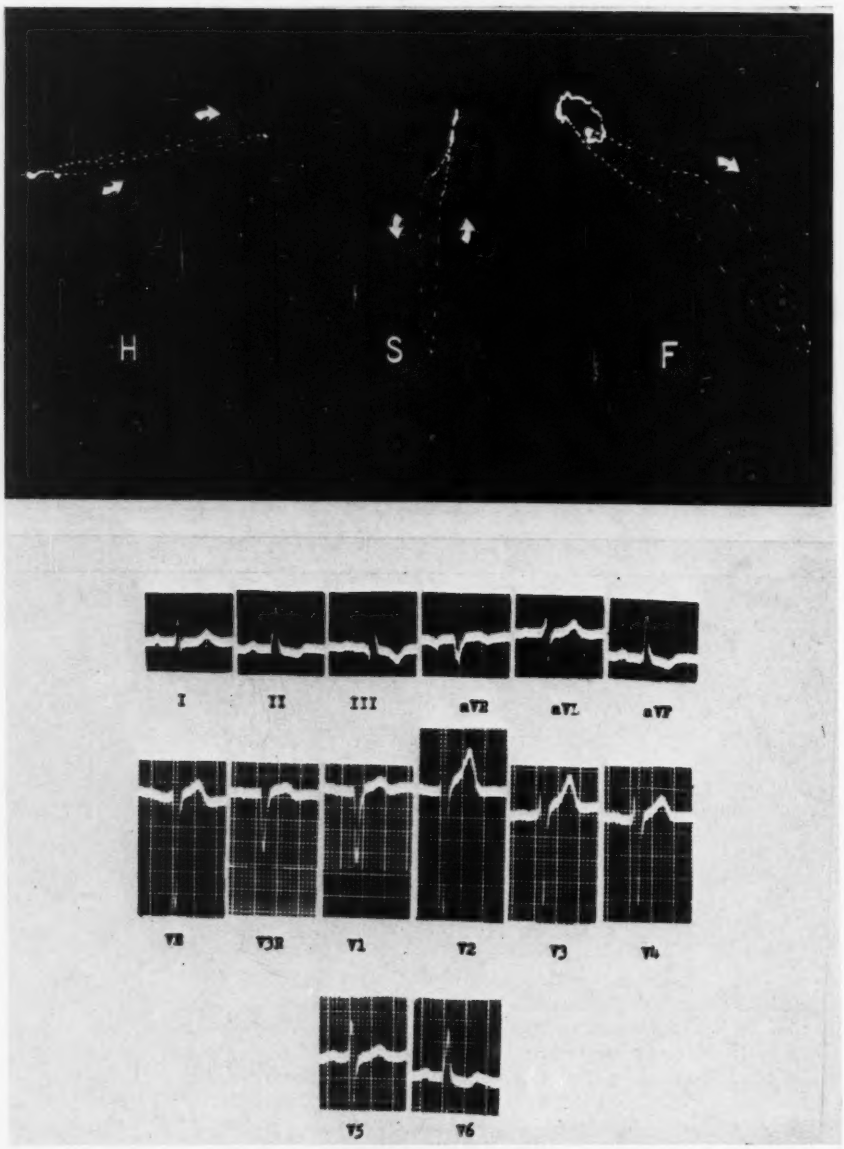

Figure 8

Vectorcardiogram and electrocardiogram in case 97, table 1. The vectorcardiogram displays the diagnostic signs of anterior and septal myocardial infarction, and left ventricular hypertrophy. The electrocardiogram does not reveal any of the conventional QRS signs of left ventricular hypertrophy. Since QS deflections in V_1 occur without infarction, the electrocardiogram was not interpreted as showing infarct. Autopsy disclosed left and right ventricular hypertrophy, and anterior and septal myocardial infarction.

Table 3

Vectorcardiographic Diagnosis of Left Ventricular Hypertrophy

	Number of cases	Diagnosed by VCG	Per cent diagnosed
All cases of left ventricular hypertrophy			
Initial forces normal	103	78	76
Initial forces left, anteriorly, inferiorly	36	28	78
Total	139	106	76
Left ventricular hypertrophy without myocardial infarction and without right ventricular hypertrophy	28	21	75
Left ventricular hypertrophy with myocardial infarction and without right ventricular hypertrophy	56	53	95
Left ventricular hypertrophy with myocardial infarction and with right ventricular hypertrophy	30	24	80
Left ventricular hypertrophy with right ventricular hypertrophy and without myocardial infarction	25	8	32

lap of normal and abnormal; and there is an expected overdiagnosis of 7.3 per cent of normals.[14] The overdiagnosis of 14 per cent in this series (four of 28 cases) is not significantly higher. The expectation that this group should show better diagnostic performance than the cases of right ventricular hypertrophy is borne out by a positive diagnosis in three fourths of the cases with anatomic left ventricular hypertrophy.

Of particular interest, then, are the four cases overdiagnosed left ventricular hypertrophy and the 33 cases of anatomic left ventricular hypertrophy missed by the vectorcardiogram. Of the overdiagnoses, three were cases with myocardial infarction, the fourth was acute cor pulmonale. Although the overdiagnoses are in a small group and are not significantly in excess of predicted overdiagnosis, it is noteworthy that three of the four had myocardial infarction. Among all cases in which both left ventricular hypertrophy and infarction were present, a vectorcardiographic diagnosis of left ventricular hypertrophy was made in 90 per cent compared with 76 per cent for the entire series. These observations suggest two possibilities: first, vectorcardiographic signs of myocardial infarction are being misinterpreted as signs of left ventricular hypertrophy but because of the very high coexistence rate of myocardial infarction and left ventricular hypertrophy, a fortuitously good correlation exists; or second, the loops do indeed display left ventricular hypertrophy in 90 per cent of the cases with infarct and that an explanation must be found for the poorer performance in the cases without infarct. We believe the latter to be true and that the reason for the poorer performance is related to the presence of right ventricular hypertrophy in many of the cases. In support of this view are the following observations: (a) when the cases of left ventricular hypertrophy plus infarct are divided into those with and those without concomitant right ventricular hypertrophy, the left ventricular hypertrophy is detectable by vectorcardiogram in 95 per cent without right ventricular hypertrophy but in only 80 per cent with right ventricular hypertrophy; (b) in a prior clinically diagnosed series of 100 cases of left ventricular hypertrophy, 91 per cent were diagnosed by vectorcardiogram,[14] a figure with which the over-all diagnosis of left ventricular hypertrophy with infarct is in close agreement; (c) in the group with biventricular hypertrophy without infarct only 32 per cent of the left ventricular

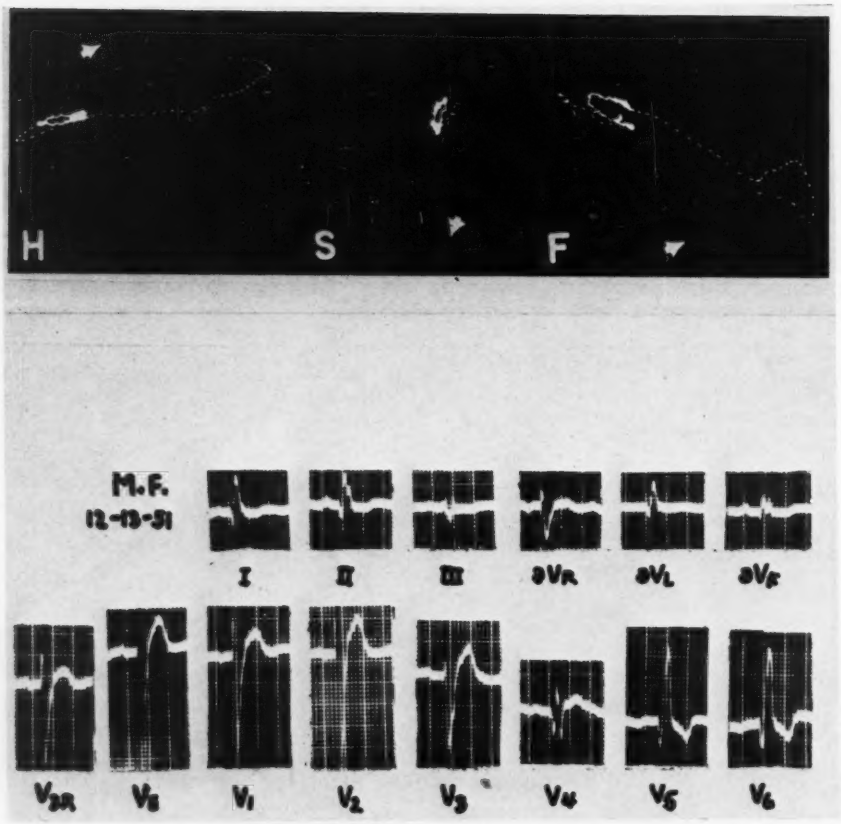

Figure 9

Vectorcardiogram and electrocardiogram in case 5, table 1. The vectorcardiogram displays the diagnostic features of anterior, inferior, and lateral myocardial infarction, and left ventricular hypertrophy. The electrocardiographic diagnosis is anterior and lateral myocardial infarction, and left ventricular hypertrophy. Autopsy revealed anterior, inferior, and lateral myocardial infarction, and left ventricular hypertrophy.

hypertrophy was detected; and (d) of the seven cases of left ventricular hypertrophy without infarct and without right ventricular hypertrophy in which left ventricular hypertrophy was not diagnosed, six had equivocal right ventricular hypertrophy.

It is not surprising that right ventricular hypertrophy should obscure the signs of left ventricular hypertrophy in the vectorcardiogram, or that left ventricular hypertrophy should mask the signs of right ventricular hypertrophy. Positional changes are important in the genesis of the vectorcardiographic signs of left ventricular hypertrophy, the changes being more posterior and horizontal orientations. Even in the complete absence of intrinsic change in the loop the reorientation is capable of increasing the greatest leftward and greatest posterior vectors of the body in the horizontal plane and the width of the superior portion of the terminal appendage in the frontal plane, the only measurements on which a diagnosis of left ventricular hypertrophy is based. The tendency in right ventricular hypertrophy for an anterior vertical loop is exactly counter to the backward horizontal position of the left ventricular hypertrophy loop. This is almost certainly the

Table 4

Correlation between Vectorcardiographic Diagnosis and Anatomic Evidence of Myocardial Lesion

	Location of lesion	Large lesions: Autopsy cases	Large lesions: VCG diagnosis	Large lesions: %	Small lesions only: Autopsy cases	Small lesions only: VCG diagnosis	Small lesions only: %	Wrong localization of infarct: Autopsy* cases	Wrong localization of infarct: VCG diagnosis	Wrong localization of infarct: %
IF ≠ LAD	High posterior wall	22	2	9	14	2	14	92	0	0
	Inferior wall	40	36	90	22	8	36	67	5	7
	Lateral wall	20	9	45	28	5	18	80	3	4
	Anterior wall	33	26	79	15	4	27	80	4	5
	Septum	33	22	67	20	9	45	73	0	0
	Infarction regardless of localization	57	51	90	20	7	35	51	1†	2
IF = LAD	High posterior wall	3	0	0	4	0	0	32	0	0
	Inferior wall	8	3	38	7	0	0	24	0	0
	Lateral wall	5	2	40	8	0	0	26	0	0
	Anterior wall	8	3	38	3	0	0	28	0	0
	Septum	8	2	25	6	0	0	25	0	0
	Infarction regardless of localization	16	5	31	5	0	0	18	0	0
All cases	High posterior wall	25	2	8	18	2	11	124	0	0
	Inferior wall	48	39	81	29	8	28	91	5	6
	Lateral wall	25	11	44	36	5	14	106	3	3
	Anterior wall	41	29	71	18	4	22	108	4	4
	Septum	41	24	59	26	9	35	100	0	0
	Infarction regardless of localization	73	56	77	25	7	28	69	1†	2

*Number of cases that had no lesion in the specified location at autopsy.

†The only case in which there was no anatomic infarct, but in which a vectorcardiographic diagnosis of infarct was made.

IF = LAD—initial forces to left, anteriorly, and inferiorly.

IF ≠ LAD—initial forces other than left, anteriorly, and inferiorly.

reason for poor performance in the diagnosis of left ventricular hypertrophy when right ventricular hypertrophy is present, and it affords an acceptable explanation for the poorer score in the group with possible right ventricular hypertrophy than in the group with infarct. That the effects of right ventricular hypertrophy and left ventricular hypertrophy can cancel each other is shown by the group in which the vectorcardiogram was normal, despite the presence of biventricular hypertrophy.

Myocardial Lesions

A vectorcardiographic diagnosis of myocardial infarction exclusive of those cases with initial forces oriented to the left, anteriorly, and inferiorly, was made in 90 per cent of the cases with a large myocardial lesion. This high degree of correlation is especially noteworthy, since diagnosis was based solely on analysis of the QRS loop. Localization was correct in 90 per cent of the inferior infarcts, 79 per cent of anterior, 67 per cent of septal, 45 per cent of lateral, and 9 per cent of high posterior wall lesions (table 4). Of the 25 cases with extensive infarction involving all five areas, a diagnosis of infarction was made in 23; one of the two undiagnosed cases had left bundle-branch block. The vectorcardiogram revealed four areas of involvement in six of these, three in 10, two in five, and one in two cases.

The excellent diagnostic performance of the vectorcardiogram raises the question of too liberal diagnostic criteria. That this is not the case is shown by the finding at autopsy of infarct in 133 of the 145 predicted locations. The remaining 12 represent nine cases

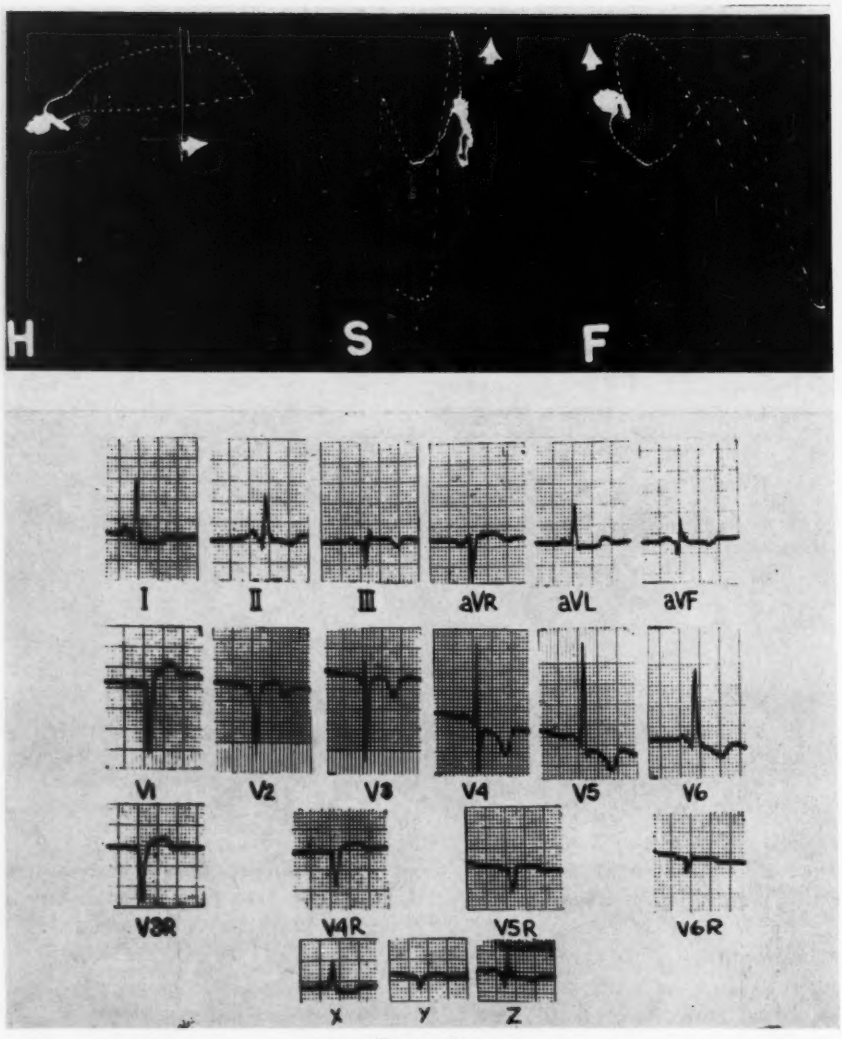

Figure 10

Vectorcardiogram and electrocardiogram in case 45, table 1. Classical vectorcardiographic signs of inferior, anterior, and septal myocardial infarction, and left ventricular hypertrophy. Electrocardiographic signs of anterior and inferior myocardial infarction, and left ventricular hypertrophy are present. Autopsy diagnoses; left and right ventricular hypertrophy, and anterior, inferior, septal, lateral, and high posterior myocardial infarction.

in which 10 errors of localization were made though the diagnosis of infarct per se was correct. In a tenth case anterior and inferior infarct and left ventricular hypertrophy were the vectorcardiographic diagnoses, but only left ventricular hypertrophy, slight coronary narrowing, and grossly normal myocardium were found; unfortunately only three microscopic sections were obtained. Thus, in the 69 cases without anatomic infarct in which an overdiagnosis of infarct could have been made, it was, in fact, made but once.

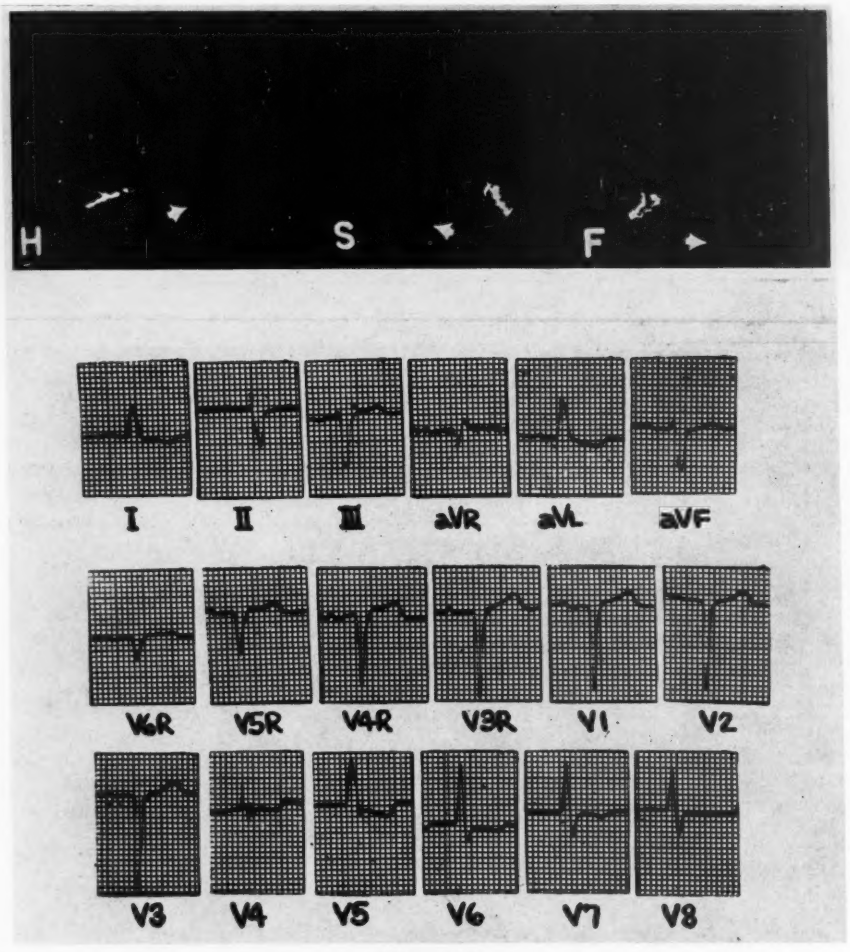

Figure 11

Vectorcardiogram and electrocardiogram in case 4, table 1. The vectorcardiogram displays the signs of anterior and septal myocardial infarction, and left ventricular hypertrophy. The electrocardiogram was interpreted as left bundle-branch block. Autopsy disclosed anterior, inferior, septal, lateral, and high posterior myocardial infarction, and left and right ventricular hypertrophy.

When left ventricular hypertrophy and myocardial infarction are simultaneously present, both diagnoses can usually be made from the vectorcardiogram. In the 86 cases in which both were present, including cases with large and small infarcts, and cases with initial forces oriented left, anteriorly, and inferiorly, the diagnosis of myocardial infarction was made in 63 per cent, and left ventricular hypertrophy in 90 per cent (tables 3 and 4). Evidently the presence of left ventricular hypertrophy does not interfere with the diagnosis of myocardial infarction.

Vectorcardiographic and electrocardiographic diagnosis of myocardial disease depends upon the demonstration that the depolarization forces have either changed from their previous pattern or differ from a pre-

Table 5

Comparison of Vectorcardiographic with Electrocardiographic Diagnosis with the Levels of Statistical Significance (χ^2 Method)

Description of group	No. of cases	V	E	P<.1	P<.05	P<.01
LVH—all cases	139	106	68			X
LVH—IF to right	103	78	47			X
MI, large, all cases	73	56	40			X
MI, septal, all cases	67	33	16			X
MI, septal, IF to right	53	31	16			X
MI, all anterior	59	33	21		X	
MI, large and small, all cases	98	63	46		X	
MI, all with IF to right	77	58	45		X	
MI, all large with IF to right	57	51	39		X	
MI, all inferior	76	46	32		X	
MI, all large inferior	47	38	26		X	
MI, all large inferior with IF right	39	35	26		X	
MI, all large septal	41	24	13		X	
MI, all large septal with IF to right	33	22	13		X	
MI, all inferior with IF to right	61	43	32	X		
MI, small septal with IF to right	20	9	3	X		

V, diagnosed by vectorcardiogram; E, by electrocardiogram.

Table 6

Criteria for Electrocardiographic Diagnosis of Left Ventricular Hypertrophy; Values Are Upper Limits of Normal

Age	Lewis Index	R aV_L	SV_1	SV_2	RV_5	RV_6	SV_1 plus RV_5 or RV_6
15-20	17	5.8	25.1	45.5	26.0	24.4	40
20-25	17	7.6	26.2	39.2	26.0	22.6	40
25-30	17	7.6	26.2	39.2	26.0	22.6	35
30-40	17	7.6	26.2	39.2	26.0	22.6	35
Over 40	17	10.1	20.0	25.4	20.7	19.0	35

Values in tenths of a millivolt.

dictable "normal." The initial forces in most normals are directed to the right and anteriorly; but in a small percentage of normals, in left bundle-branch block, in some vertical loops with clockwise rotation, in some horizontal loops with counterclockwise rotation, in the Wolff-Parkinson-White syndrome, and in some cases of myocardial infarction, the earliest forces are oriented to the left, anteriorly, and inferiorly. Such initial forces occur with sufficient frequency in other conditions to preclude their use as a sign of infarction. In the case of left bundle-branch block, there is the additional difficulty that depolarization of the peri-infarction myocardium occurs late, at a time when the "normal" is not clearly defined.

It is not surprising, therefore, that few diagnoses of infarct were made in cases with initial forces oriented left, anteriorly, and inferiorly (fig. 5). All the cases in which the diagnosis of myocardial infarction was made had large infarction; one of the cases with left bundle-branch block in which myocardial infarction was diagnosed (case 136) was left bundle-branch block masquerading as right bundle-branch block. This pattern indicates septal and posterolateral infarct.[16]

Pulmonary Embolism (Acute Cor Pulmonale)

Of the 14 cases with acute pulmonary lesions at autopsy, the vectorcardiogram was diagnostic in four. The electrocardiogram was diagnostic in only one of these four cases, and in none of the remaining 10. In three of the

four cases acute cor pulmonale was the only vectorcardiographic diagnosis. In the fourth case the pattern of left ventricular hypertrophy was also present, but this proved to be an overdiagnosis. Two hearts were anatomically normal, one had left ventricular hypertrophy and one had biventricular hypertrophy. None of these cases had infarction. On the other hand, only one of the 10 cases in which the diagnosis was missed had a normal vectorcardiogram, and in this case the heart was anatomically normal. In the nine remaining cases the vectorcardiogram showed some abnormality, either right or left ventricular hypertrophy, or both, or myocardial infarction, and in each case autopsy revealed one or more cardiac abnormalities. Infarction was present in seven of the 10 cases. This small series suggests that myocardial infarction may interfere with the development of vectorcardiographic signs of acute cor pulmonale.

Vectorcardiographic Versus Electrocardiographic Diagnosis

We hoped, when we undertook the study of vectorcardiography, that a diagnostic performance better than that obtained with standard electrocardiography[14, 21-30] might be possible. In all diagnostic categories this has proved to be the case; in no instance has this been at the expense of greater overdiagnosis.

Table 5 lists those categories in which vectorcardiographic superiority is significant at the 1, 5, and 10 per cent levels.

Summary and Conclusions

A correlative study of vectorcardiographic diagnosis and autopsy findings was carried out in 167 consecutive cases.

The vectorcardiographic diagnosis was compared to the electrocardiographic diagnosis in relation to true positive diagnosis and false diagnosis. False diagnosis was uncommon in this series. The over-all diagnostic performance of the vectorcardiogram was superior to that of the electrocardiogram.

A vectorcardiographic diagnosis of myocardial infarction was made in 90 per cent of the cases with a large lesion, and 35 per cent of those with a small lesion, exclusive of cases with initial forces oriented to the left, anteriorly, and inferiorly. Myocardial infarction may be responsible for the orientation of initial forces to the left, anteriorly, and inferiorly (about half of these are cases of left bundle-branch block) but, since this occurs in other conditions, a diagnosis of myocardial infarction cannot be made on this basis alone.

The concomitant presence of left ventricular hypertrophy did not interfere with the vectorcardiographic diagnosis of infarction.

In the presence of extensive disease (involvment of five areas) infarction was recognized in 92 per cent of the cases.

The diagnostic performance for left ventricular hypertrophy was almost as good as that for myocardial infarction. Concomitant right ventricular hypertrophy interferes with the vectorcardiographic diagnosis of left ventricular hypertrophy, but myocardial infarction does not.

Right ventricular hypertrophy was recognized only in cases with moderate or marked increase in right wall thickness.

The vectorcardiogram provides a useful addition to our diagnostic armamentarium and should be made available on a clinical basis when the electrocardiogram is equivocal or at variance with the clinical picture.

Criteria for electrocardiographic and vectorcardiographic diagnosis are given in Appendix I.

Illustrative vectorcardiograms and electrocardiograms are presented in Appendix II.

Appendix I

Criteria for Vectorcardiographic and Electrocardiographic Diagnosis

Left Ventricular Hypertrophy

Vectorcardiographic diagnosis of left ventricular hypertrophy was made when the maximum leftward vector of the body in the horizontal plane exceeded 0.68 mv.; when posterior vectors of the body in the horizontal plane exceeded 0.095 mv. more than 0.045 second after onset of the QRS; or when the width of the superior portion of the terminal appendage in the frontal plane exceeded 0.185 mv.[44]

Electrocardiographic diagnosis of left ventricular hypertrophy was made when any of the values listed in table 6 was exceeded.[22, 23, 34, 35]

Right Ventricular Hypertrophy

A vectorcardiographic diagnosis of right ventricular hypertrophy was made when the body of the loop in the horizontal plane was anterior and clockwise and the body in the frontal plane vertical and clockwise.[15]

An electrocardiographic diagnosis of right ventricular hypertrophy was made when any of the following was found:[21, 26]

1. Axis $> +110°$.
2. R/S ratio in $V_1 > 1$ provided $R > 5$ mm.
3. $RV_1 > 10$ mm. in absence of right bundle-branch block.
4. Reversal of precordial pattern.

Acute Cor Pulmonale

A vectorcardiographic diagnosis of acute cor pulmonale was made when a large rightward-posterior-superior terminal appendage was present in a clockwise frontal plane loop, which occupied a semi-horizontal or horizontal position.[15]

An electrocardiographic diagnosis of acute cor pulmonale was made on the basis of terminal S waves in leads I, aV_L, aV_F, and Ve with terminal R waves in aV_R and the right precordial leads.[27, 28]

Myocardial Infarction

Anterior. A vectorcardiographic diagnosis of anterior myocardial infarction was made when in the horizontal plane the loop was entirely posterior, when the loop was partly or wholly posterior and clockwise, or when posterior forces of the body exceeded 0.095 mv. within the first 0.045 second after onset of the QRS.[11, 21, 23]

An electrocardiographic diagnosis of anterior myocardial infarction was based upon presence of abnormal Q or QS deflections in the precordial leads.

Inferior. A vectorcardiographic diagnosis of inferior infarct was made when initial or early superior forces in the frontal plane exceeded 0.12 mv., when the superior/inferior ratio exceeded 0.13, when the sweep was clockwise and exceeded 0.065 mv. or lasted longer than 0.0275 second.[10]

Electrocardiographic diagnosis of inferior infarct was made when abnormal Q waves were found in II, III, and aV_F.

Septal. Septal infarct was diagnosed when the initial vectors were posterior in the vectorcardiogram, and when there was a Q wave or QS deflection in Ve of the scalar electrocardiogram.

Lateral. Lateral myocardial infarction was diagnosed when the rightward initial forces of the vectorcardiogram exceeded 0.07 mv. or when the right/left ratio was greater than 0.15.[9]

An electrocardiographic diagnosis of lateral infarct was made when abnormal Q waves of QS deflections were present in I, aV_L, V_5, and V_6.

High Posterior. Infarct in this location was not recognized in any electrocardiogram. Vectorcardiographic diagnosis was based upon anterior displacement of the early forces exceeding 0.055 mv.[9]

Appendix II

Illustrative Cases

The body of the QRS loop in the horizontal projection shown in figure 6 (case 76, table 1) is posterior suggesting infarct or left ventricular hypertrophy; both were present. The abnormal width of the terminal appendage in the frontal projection is diagnostic of left ventricular hypertrophy, and the excessive posterior displacement early in the QRS loop in the horizontal projection indicates anterior infarction. The electrocardiogram revealed only left ventricular hypertrophy.

Excessive posterior displacement in figure 7 (case 162, table 1) occurs late and is therefore indicative of left ventricular hypertrophy. The latter is also shown by the abnormal width of the terminal appendage in the frontal projection. None of the conventional indices of left ventricular hypertrophy is met in the electrocardiogram, which simulates right bundle-branch block. Absence of a terminal R′ deflection in lead Ve is rare in right bundle-branch block, and a diagnosis of this conduction defect was not made.[22, fig. 67]

A vectorcardiographic diagnosis of anterior and septal infarction and left ventricular hypertrophy was made in figure 8 (case 97, table 1). The QRS loop in the horizontal projection is entirely posterior, which signifies infarction almost without exception; in a posterior loop the figure-of-eight configuration has the same significance as clockwise inscription, i.e., anterior infarction. The latter is also suggested by the leftward orientation of the initial forces. Posterior displacement of the initial forces indicates septal infarction. A diagnosis of left ventricular hypertrophy was made on the basis of excessive posterior displacement in the horizontal projection late in the QRS loop.

The electrocardiogram does not reveal any QRS abnormalities of infarction or conventional QRS signs of left ventricular hypertrophy.

The early superiorly oriented vectors in the frontal projection of figure 9 (case 5, table 1) were considered diagnostic of inferior infarction, despite their counterclockwise inscription. The latter occurs when there is a lateral wall as well as a posterior wall lesion. Diagnosis of the lateral wall infarction is supported by the abnormal ratio of rightward initial forces to the leftward displacement of the body. The earliest vectors are inferiorly oriented but reverse their direction to superior orientation after two or three time markings. Beyond this point the large sweep of the superior vectors and the abnormal ratio between the superior vectors and the inferior displacement of the body (superior-inferior ratio) are diagnostic of an inferior wall lesion.[23] Inferior

orientation of the earliest vectors tends to obscure the electrocardiographic diagnosis of inferior wall infarction, as was true in this case.

A diagnosis of anterior infarction was made on the basis of clockwise initial forces in the horizontal plane and a clockwise completely posterior body of QRS.[31] The diagnosis of left ventricular hypertrophy was made because of abnormally large posterior forces occurring late in the cardiac cycle.

The electrocardiogram was interpreted as left ventricular hypertrophy and anterior and lateral myocardial infarction.

A classical vectorcardiographic pattern of inferior myocardial infarction is shown in figure 10 (case 45, table 1). The beginning of the frontal projection displays abnormally large superior forces that are inscribed in a clockwise direction with a large sweep, and the superior-inferior ratio is abnormally large. The beginning of the loop in the sagittal projection is counterclockwise.

The clockwise initial forces and the completely posterior QRS loop in the horizontal projection are diagnostic of anterior myocardial infarction, and the posterior initial forces indicate septal infarction.

Left ventricular hypertrophy was diagnosed on the basis of abnormal maximum posterior displacement occurring late in the cardiac cycle.*

The electrocardiogram was interpreted as left ventricular hypertrophy, and anterior and inferior myocardial infarction.

Figure 11 (case 4, table 1) displays the patterns of left ventricular hypertrophy and anterior and septal myocardial infarction. The abnormal width of the terminal appendage in the frontal projection is characteristic of left ventricular hypertrophy. The excessive posterior displacement of the QRS loop early in the cardiac cycle and the completely posterior loop indicate anterior myocardial infarction. Septal infarction is indicated by the posterior orientation of the initial forces.

The electrocardiogram was interpreted as left bundle-branch block.

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*In this vectorcardiogram there are 800 time markings per second, in all the others there are 400.

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On Cardiac Murmurs

By AUSTIN FLINT, M.D.

The clinical study of cardiac murmurs, within the last few years, has led to our present knowledge of the diagnosis of valvular lesions of the heart. By means of the organic murmurs it is positively ascertained that lesions exist in cases in which, without taking cognizance of the murmurs, the existence of lesions could only be guessed at. The absence of the organic murmurs, on the other hand, enables us generally to conclude with positiveness that valvular lesions do not exist. As a rule, to which there are but few exceptions, these lesions may be excluded, if there be no murmur.—*Am. J. M. Sc.* n.s. **44**: 29, 1862.

Prognosis of Men Returning to Work after First Myocardial Infarction

By GEORGE E. DIMOND, M.D.

THE PROGNOSIS after the first myocardial infarction is usually based on those living for 1 or 2 months beyond the acute attack. This paper is to report the prognosis of 202 railway operating employees who returned to full-time work following their first myocardial infarction.

Cole and associates[1] found that of 285 patients who lived more than 2 months after their initial infarction, 66 per cent survived 5 years and 43 per cent 10 years. In a similar study Weiss and Gray[2] reported on 484 patients and 61 per cent lived 5 years. Weiss[3] followed 211 cases 10 years or more: 60 per cent lived 5 years and 37 per cent 10 years. Honey and Truelove[4] reporting 348 cases indicated 61 per cent 5-year and 32 per cent 10-year survival rates. Juergens and associates[5] found that of 224 patients who survived 1 month following the initial attack, 55 per cent lived 5 years and 29 per cent 10 years.

Authors agree that those patients capable of returning to full-time activity after the initial infarct have the better prognosis. Fifty-nine of the 285 patients reported by Cole and associates[1] returned to full activity and 71 per cent lived 10 years or more. Seventy-one of those followed by Juergens and associates[5] returned to complete activity and 73 per cent lived 5 years. In a 5-year follow-up of 431 men returning to some form of gainful employment after their initial myocardial infarction, Weiss and Weiss[6] found that 22 per cent were dead and an additional 11 per cent had retired.

Material and Methods

Coronary artery disease among operating personnel became a major concern of the New York Central Railroad Medical Department during 1935 to 1940. A study of 1,000 consecutive deaths in operating personnel indicated that 22 per cent of these deaths were clinically attributable to coronary heart disease. An increasing number of men who survived their initial myocardial infarction were applying for return to service in the operating division. It was the practice of the medical director to return these men to work, if functional recovery was good, but engineers were removed from passenger service and restricted to yard work. Some of these restricted engineers, having worked a few years in the yard without further disability, were demanding restoration of their road rights.

The medical director in 1940 initiated a series of discussions among the chief surgeons of the railroad and consulting cardiologists, concerning the problem of coronary artery disease in operating train personnel. A system-wide policy resulted from these discussions and stipulated that men applying for return to service after having a myocardial infarction were to be examined by an internist. If this examination indicated a good functional recovery, the man was returned to work and re-examined periodically. Engineers were routinely and permanently restricted to yard service after a myocardial infarction. This policy has been followed since 1940.

Two hundred and two men were selected for this study. Characteristic electrocardiograms, a definite clinical history, and date of onset of the first infarct were requirements. Those with coexistent valvular heart disease were excluded. The period during which the first myocardial infarction occurred was between July 1, 1940, and July 1, 1955. All men were followed to July 1, 1960. Ninety-seven of the 202 men had their initial infarct between July 1, 1940, and July 1, 1950, and are the basis of the 10-year survival rates.

All men had been given pre-employment examinations and routine periodic examinations after their employment. These records gave information concerning health prior to the initial myocardial infarction.

With the exception of engineers the majority of these employees returned to their usual work. Many took easier assignments in accordance with the seniority rules.

Causes of death were based on reports from attending physicians, death certificates, and records of The National Railroad Retirement Board. A number of these deaths were sudden or relatively sudden, and the diagnosis of recurrent myocardial infarction on the death certificate was

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Table 1

Causes of Eighty-four Deaths

Cause	Number
Recurrent clinical myocardial infarction	55 (65%)
Myocardial failure	10
Malignancy	7
Cerebral vascular accident	1
Miscellaneous	3
Unknown	8

Table 2

Yearly Incidence of Second Clinical Myocardial Infarctions Five Years after Initial Infarction

Years after onset of initial infarct	Number surviving second infarct	Number of fatal second clinical infarcts	Total
1	7	2	9
2	5	4	9
3	8	2	10
4	5	8	13
5	2	5	7

possibly based only on history. Necropsy data on patients dying within minutes or a few hours after an episode of chest pain may fail to reveal a recurrent infarction, and it is assumed that death is due to myocardial ischemia that initiates a fatal cardiac arrhythmia.[5] In this report those dying suddenly are included in the group described as having second clinical infarctions.

Results

At the conclusion of the period of observation on July 1, 1960, 118 men were living and 84 were dead. The average survival time to date is 8 years. Seventy-three men are still actively employed, having had their initial infarct at an average age of 51. Fifty men who incurred their first infarct at average age of 60 retired in the usual manner between ages 65 and 70. Thirty-nine men returned to work and subsequently retired on disability pension before reaching age 65. Forty men died while still actively employed and these men survived an average of only 4½ years after the initial infarction.

One hundred sixty-eight men (83 per cent) survived 5 years. During the first 5 years after the initial infarct 49 men sustained a second clinical infarction. Sixteen men although living at the end of 5 years, had medically retired before age 65 for cardiac causes. Included in this group are seven who retired following a second infarction and the remainder retired because of incapacitating angina or myocardial failure. At the end of 5 years 17 per cent of the 202 men were dead, 24 per cent had sustained a second clinical infarct, and in addition to those dead 8 per cent were totally disabled by cardiac disease.

The 5-year survival rates for the 97 men followed 10 years or more were the same as for the total group. Fifty-seven per cent lived 10 years or longer. During the 10 years after the initial infarct 45 per cent had a second clinical infarction. Eight per cent of the men, although living past 10 years, were totally disabled by cardiac disease.

The causes of 84 deaths are listed in table 1. Sixty-five per cent of the deaths were due to second or third clinical myocardial infarctions. Recurrent myocardial infarction or a sudden type of cardiac death are the most common causes of death in men who survive the initial infarction.

Juergens and associates[5] found that myocardial failure without second infarction was the cause of death in 21 per cent of 79 cases at necropsy. Only 10 men in this series died of myocardial failure. Five of these survived a second myocardial infarction by 2 months or more but subsequently died of myocardial failure.

Eighty-two second clinical myocardial infarctions have occurred in this series to date. Thirty-six survived, giving a mortality rate for the second infarct of 56 per cent. Cole and associates[1] found that during the first 5 years after the initial infarction a second episode was fatal in 87 per cent, and in those surviving beyond 5 years the second infarct was fatal in 70 per cent. Of the 36 men who lived following the second infarction, 10 retired and 26 returned to full-time railroad employment. Twelve men who survived their second infarct subsequently had a third, and only one survived the third infarction.

The yearly incidence of the second clinical

Table 3

Five-Year Prognosis in Relation to Age at Initial Infarction

Age at onset, years	Total	Lived 5 years or more	Had second clinical infarct within 5 years
30-39	7	7 (100%)	2 (28%)
40-49	44	36 (82%)	13 (29%)
50-59	105	89 (85%)	25 (24%)
60-69	46	36 (80%)	9 (20%)

Table 4

Ten-Year Prognosis in Relation to Age at Initial Infarction

Age at onset, years	Total	Lived 10 years or more	Had second clinical infarct within 10 years
30-49	25	17 (68%)	11 (44%)
50-59	47	25 (53%)	24 (51%)
60-69	25	12 (48%)	9 (36%)

myocardial infarctions occurring in the first 5 years after the initial attack is given in table 2. With some yearly fluctuations, 5 per cent of the second clinical infarcts occurred annually. During the first 3 years after the initial infarct less than one third of the second infarcts were fatal. This is in contrast to the prognosis described for those surviving their initial infarct by 1 or 2 months in whom the first and second years accounted for the greatest number of deaths.[4]

Younger patients have been observed to survive for longer periods after the first infarct.[1, 5] This better prognosis is not evident when the normal life expectancy of the different age groups is considered. Honey and Truelove[4] indicated that the chance of death in patients over 60 making a good recovery from the initial infarction was about the same as that of the general population over 60. In those under 60 the mortality rates were approximately 3 times the normal expectations within 5 years after the first infarction. This increased mortality rate was almost entirely due to recurrent myocardial infarction.

In this study the average age at the time of the initial infarct was 55 years. Sixty-eight per cent of the men were under 60 and none was over 70. The 5-year and 10-year prognosis in relation to age is indicated in tables 3 and 4. The differences are not of statistical significance. Younger men are more likely to sustain a second infarction and older men are less likely to survive 10 years or more, being more subject to death from noncardiac causes.

Table 5 summarizes the factors that might influence the prognosis. Hypertension was defined as blood pressure over 150/90 for a period of 3 years or more preceding the initial infarct. Fifty men had this type of hypertension. The average age of these men was 55 years. The average duration of the hypertension was 10 years. The complication of hypertension is associated with an adverse 5-year prognosis.

Thirty-two men were considered overweight preceding their initial infarct, their weight exceeding by 25 pounds the desirable weight for men 25 years of age or over with a large frame.[7] One half of the overweight men had associated hypertension. The increased mortality rates and second clinical infarcts noted in these men are not statistically significant.

The initial infarct was predominantly located in the posterior ventricle in 111 cases, the anterior in 83, five were lateral infarcts, and three were both anterior and posterior in location. The frequency of posterior infarction in this report is in contrast to the usual finding of a greater involvement of the anterior location.[1, 5] This suggests that those men with posterior wall infarcts are more

Table 5

Five-Year Prognosis in Relation to Hypertension, Obesity, Location and Extent of Initial Infarct, and Cardiac Enlargement after Initial Infarct

Factor	Alternatives	Total	Lived 5 years or more	Had second clinical infarct within 5 years
Hypertension prior to infarct	Present	50	38 (76%)	17 (34%)
	Absent	152	130 (88%)	32 (21%)
Overweight prior to infarct	Present	32	24 (75%)	12 (37%)
	Absent	170	144 (85%)	37 (22%)
Location of initial infarct	Anterior	83	70 (84%)	21 (25%)
	Posterior	111	91 (83%)	26 (23%)
Extent of initial infarct	Transmural	164	136 (83%)	39 (24%)
	Subendocardial	38	32 (84%)	10 (26%)
Cardiac enlargement after initial infarct	Present	28	20 (71%)	12 (43%)
	Absent	174	152 (87%)	37 (21%)

likely to make a good functional recovery. The location of the initial infarct had no influence on the 5-year prognosis.

Electrocardiographically 164 initial infarcts were transmural and 38 were subendocardial. Cole and associates[1] found a better prognosis for long-term survival in people with subendocardial infarction. In this series the survival rates and the incidence of recurrent clinical infarctions at the end of 5 years are the same for both groups.

Twenty-eight men had cardiac enlargement, confirmed by chest x-ray or fluoroscopy, on return to service following the first infarct. Cardiac enlargement after the initial myocardial infarction had an adverse effect on the 5-year prognosis.

During the period of this study 51 men were examined following their initial myocardial infarction and advised to retire. The average age of these men was 59 years. The majority had angina pectoris or myocardial damage which precluded return to a vigorous occupation. Only 28 (55 per cent) of these men lived 5 years or more.

Discussion

It should be emphasized that the men in this study are a highly selected group. Prior to their initial myocardial infarction they had a pre-employment examination and routine periodic examinations. These examinations largely eliminated diabetes, severe hypertension, and gross obesity as factors in this study.

The prognosis for men able to return to work is better than that for those retiring. This better prognosis is due in part to a lesser incidence of myocardial failure and a better ability to survive a second infarction. Weiss and Weiss[6] indicated that sudden or relatively sudden death occurred in 25 per cent of their patients who died following return to work. Twenty-four per cent of the patients in this series were subject to recurrent clinical infarctions within 5 years. These figures emphasize the necessity of restriction to work where sudden death or disability will not be hazardous to others.

The time elapsed after the initial infarction cannot be regarded as a factor in freedom from future myocardial infarcts. Of the second clinical infarcts, 44 occurred in the 97 cases followed 10 years, 23 in the first 5 years and 21 in the second 5 years. The second clinical infarcts during the first 5 years were fatal in 52 per cent and the infarcts in the second 5 years were fatal in 80 per cent.

Some factors adversely influence the prognosis following the first myocardial infarction.

The prognosis is subject, however, to the well-known, bizarre, and unpredictable nature of the disease. Authors[1, 6] agree that no single physical finding or test can be a prognostic guide. Pending better methods to estimate the efficiency of the coronary circulation, prognosis can be best judged by the degree of functional recovery.

Periodic examinations are of no value in predicting the occurrence of the second infarct. Re-examinations are of value in detecting the earlier evidences of myocardial failure, the symptoms and electrocardiographic signs of increasing myocardial ischemia, and in controlling factors that adversely effect the prognosis.

None of the men reported in this series was treated with anticoagulants following the first infarct. Four men now working following their second infarct are taking anticoagulants.

Summary

The 5-year prognosis of 202 railway operating employees returning to full-time work after their initial myocardial infarction and the 10-year survival rates of 97 of these men have been described. The 5-year survival rate was 83 per cent and the 10-year survival rate was 57 per cent.

Twenty-five per cent of these men died or were totally disabled at the end of 5 years and 50 per cent at the end of 10 years. The cause of death or disability following the initial infarction was largely due to recurrent myocardial infarction.

The prognosis for men returning to full-time activity after the first myocardial infarction is better than that reported for those surviving without consideration for their functional recovery. This better prognosis is not due to freedom from second infarctions but to a decreased incidence of myocardial failure and the ability better to survive and tolerate a second infarction.

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Introspection

Perpetual self-inspection leads to spiritual hypochondriasis.—Oliver Wendell Holmes, M.D. *Pages from an Old Volume of Life,* 1883.

Auscultatory Findings in Patients with a Small Ventricular Septal Defect

By LUKE VAN DER HAUWAERT, M.D., AND ALEXANDER S. NADAS, M.D.

THE auscultatory and phonocardiographic characteristics of ventricular septal defects have been the subject of several studies,[1-5] none of them dealing specifically with the features of small defects. The present study represents an attempt to define the phonocardiographic pattern of ventricular septal defect with a small left-to-right shunt and normal pulmonary artery pressure. It was hoped that this might provide the clinician with a means of differentiating the murmur of a small ventricular septal defect from the "innocent" or "functional" murmur and from the murmur of mild infundibular pulmonic stenosis.

Material and Methods

Twenty-one patients with small ventricular septal defects form the basis of this report. All were proved at cardiac catheterization to have a left-to-right shunt resulting in a pulmonary blood flow less than twice the systemic flow. Pulmonary artery pressures were normal in all. Twelve patients (group 1) had identical right ventricular and pulmonary artery systolic pressures and nine (group 2) had a slight gradient of less than 20 mm. Hg across the infundibulum of the right ventricular outflow tract. Ten patients were male, 11 were female. Their ages varied from 1 to 22 years. They were all completely asymptomatic and had normal electrocardiograms and roentgenograms.

All patients were carefully examined and phonocardiograms were obtained in all. In two instances the Sanborn Twin-Beam apparatus was used; in the rest of the patients the phonocardiograms were obtained by means of a new Sanborn Poly-Beam recorder.* The tracings were recorded in the recumbent position, at a paper speed of 100 mm. per second. As reference tracings the electrocardiogram, the carotid artery pulsation, the jugular venous pressure tracing, and the linear apex cardiogram were used. The chest expansions during respiration were registered simultaneously with phonocardiograms at the second right and second left intercostal space, in order to elucidate the respiratory changes in the splitting of the second sound. The aortic component of the second sound was identified by means of the dicrotic notch on the carotid artery tracing, allowance being made for a lag of .03 to .04 second between the sound and pressure phenomena. All other tracings were obtained while expiration was held. The intensity of the murmurs was judged exclusively on auscultation (grade 1 to 6 according to Levine[6]), since the phonocardiograms were not thought to be adequate for such comparison.

The diagnosis of ventricular septal defect was based on oxygen saturation data in 15 of 21 instances. In these cases a minimum of 5 per cent increase in oxygen saturation was found at the ventricular level in at least two sets of blood samples. In the remaining six children the oxygen saturation data were not conclusive enough for the diagnosis of ventricular septal defect. The following ancillary methods were used in these cases:

1. *Cinecardiography* (one patient). In a 1-year-old infant, the catheter was advanced from the right atrium through the foramen ovale, to the left atrium, and into the left ventricle. A cineangiogram, with injection of contrast medium (Hypaque 90 per cent) into the left ventricle, clearly outlined the ventricular septal defect.
2. *Indicator-dilution curves* (three patients). In one child the catheter was passed in a retrograde fashion from the femoral artery into the left ventricle. Indocyanine green was injected and blood samples were obtained from the right heart cavities. The early appearance of the dye in the pulmonary artery and right ventricle proved the existence of a ventricular septal defect. In two additional patients dye was injected through a catheter into the peripheral pulmonary artery; this was assumed to be com-

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*The Sanborn Crystal microphone (Model 350-1700-C10) and the Sanborn Heart Sound Preamplifier (Model 350-1700B) in connection with a 4-channel Sanborn Poly-Beam recorder (Model 550M) were used.

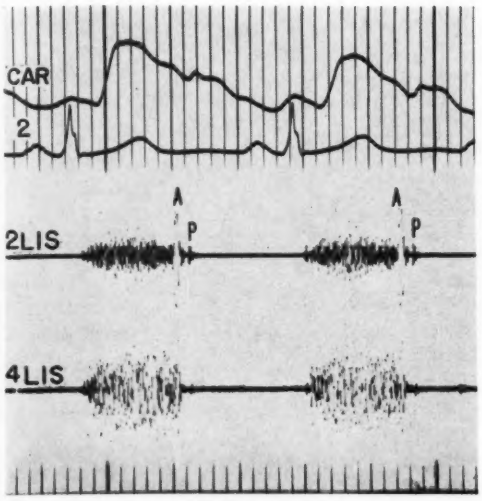

Figure 1

Plateau-shaped, pansystolic murmur. The interval between the aortic (A) and pulmonic closure sound (P) is 0.04 second. CAR, external carotid artery tracing; 2, standard lead II of the electrocardiogram; 2 and 4 LIS, second and fourth left intercostal space parasternally. Time scale with 0.04 second between lines.

parable to an injection directly into the left atrium. A second catheter was used to sample the pulmonary artery and the chambers of the right heart. The early appearance of the dye in the right ventricle, as compared to the right atrium and superior vena cava, suggested the presence of a left-to-right shunt at a ventricular level.[7]

3. *Intracardiac phonocardiography* (two patients). The diagnostic significance of this technic is based on the fact that a murmur is maximal at its site of origin and is virtually absent proximally. Thus, in the case of a patient with a ventricular septal defect, the murmur is of maximal intensity at the ventricular level, is absent in the right atrium,[8, 9] and is transmitted slightly to the main pulmonary artery. In two patients intracardiac phonocardiography served as the only evidence of the presence of a ventricular septal defect, whereas in three additional children it confirmed diagnoses based on oxygen saturation data.

Results

Group 1

Among the 12 patients without any gradient across the infundibulum, the murmur was maximal at the fourth left intercostal space parasternally in seven and at the third left intercostal space in five. The intensity of the murmur was grade III or IV in most instances. There was one patient with a grade II and one with a grade V murmur.

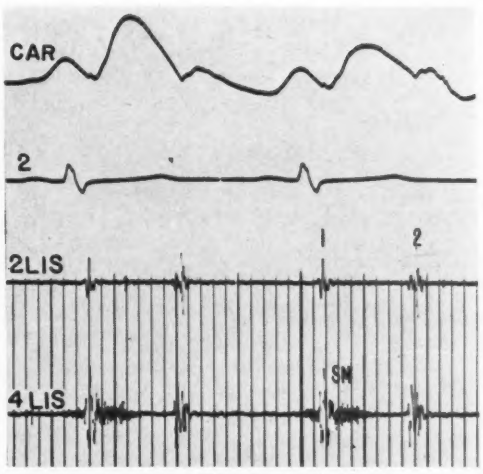

Figure 2

Early systolic decrescendo murmur, restricted to the first half of systole.

Phonocardiographically, the murmur was found to be pansystolic and plateau-shaped in seven instances, starting with the first sound and extending up to or just beyond the aortic component of the second sound (fig. 1). In three cases the murmur was restricted to the first half of systole (fig. 2). On auscultation these early systolic decrescendo murmurs had a high-pitched quality and their short duration could readily be appreciated. In the remaining two cases without infundibular gradient, the murmur was clearly diamond-shaped, extending slightly beyond the aortic component of the second sound. One of these murmurs had a midsystolic, the other a late systolic peak (figs. 3 and 4).

The second sound was best heard at the second left intercostal space and was of normal intensity in all patients. In some of the children with a pansystolic murmur the splitting of the second sound was difficult to appreciate. On the phonocardiograms, by contrast, the splitting was visible in all in-

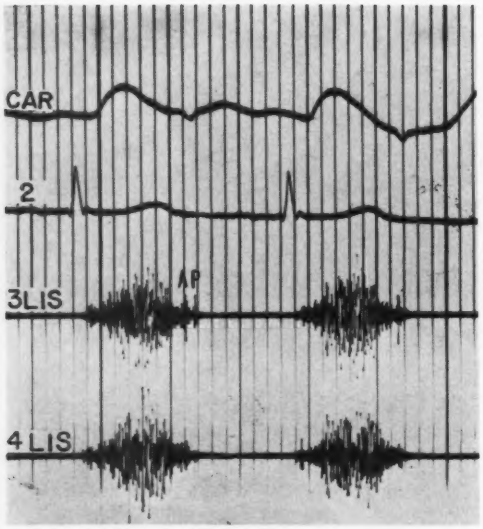

Figure 3

Diamond-shaped murmur with midsystolic peak in a patient without infundibular or valvular gradient.

stances. The difference between the auscultatory and phonocardiographic findings, in this respect, may have been because the intense pansystolic murmur obscured the aortic component of the second sound. The interval between the aortic and pulmonary component was .02 or .03 second in held expiration in eight children, and in the four remaining patients .04 or .05 second (fig. 5). An inspiratory increase in the degree of splitting was noted in the 10 patients in whom a satisfactory respiratory tracing was obtained.

In only one patient was a faint apical middiastolic rumble registered. In one child a prominent diastolic "click" was heard and registered at the fourth left intercostal space. Because of its timing (.18 to .19 second after the second sound) and its high-pitched quality, it was thought not to represent a third sound.

Intracardiac phonocardiograms were obtained in three children and showed a pansystolic murmur in the right ventricle. No murmur was demonstrated in the right atrium, but a faint ejection murmur was registered in the main pulmonary artery.

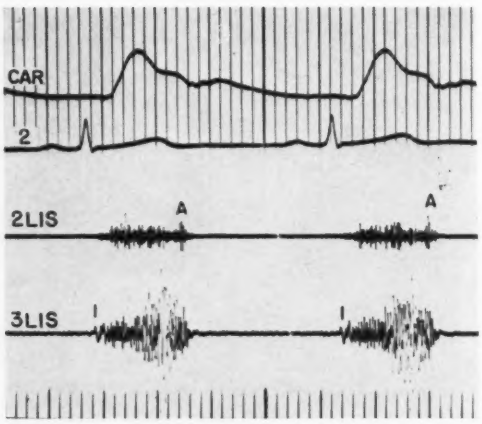

Figure 4

Diamond-shaped murmur with late systolic peak in a patient without infundibular or valvular gradient.

Group 2

All nine patients in this group showed a systolic pressure gradient at the infundibular level. The gradient varied from 6 to 18 mm. Hg and was thought not to be of hemodynamic significance.

At auscultation the murmurs tended to be somewhat louder than in the previous group; they were all at least grade III in intensity and six of them were estimated to be grade V or VI. The point of maximal intensity was at the third or fourth left intercostal space parasternally.

The pattern of the murmur was analyzed on the phonocardiograms; in four cases it was pansystolic and plateau-shaped, and in five diamond-shaped. Among the latter there were three with a midsystolic and one each with an early and late systolic peak (fig. 6).

The second sound was of normal intensity with a rather wide, easily audible split in most patients. The phonocardiograms showed the splitting in held expiration to be normal in two and wide (.04 second or more) in seven cases. In the eight patients with an adequate respiratory tracing the splitting increased on inspiration. In most instances the pulmonary component of the second sound was slightly less intense than the aortic component.

In two children intracardiac phonocardio-

grams were available. In one, a patient with a gradient of 16 mm. Hg at the infundibular level, a loud diamond-shaped murmur was recorded in the main pulmonary artery whereas the murmur in the body of the right ventricle was more pansystolic. In the other, a patient who had a 6-mm. gradient, only a faint ejection murmur was registered in the pulmonary artery and a loud pansystolic murmur was present in the outflow tract of the right ventricle.

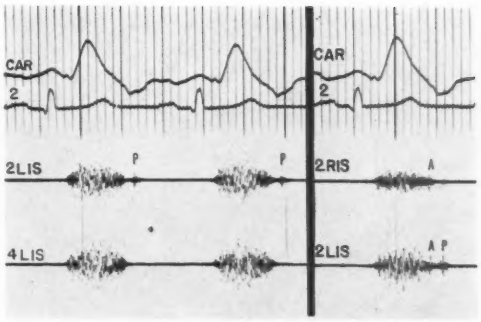

Figure 5

Wide splitting of the second sound with an interval of 0.06 second between the aortic (A) and pulmonic (P) valve closure, in a patient without infundibular or valvular gradient. The aortic closure sound, which occurred 0.04 second before the carotid dicrotic notch, is obscured by the systolic murmur at the fourth left intercostal space but is well visualized at the second right intercostal space and at the second left intercostal space in the second half of the tracing.

Discussion

The typical murmur of a ventricular septal defect is considered to be loud, high-pitched, pansystolic, and maximal at the lower left sternal border. Phonocardiograms are reported to show that the murmur starts with the first sound, is plateau-shaped, and extends to the aortic closure or slightly beyond it.[1-5] The long duration of the murmur is based on the persistent gradient between the right and left ventricle throughout systole. The second sound is thought to be normally split and to vary with respiration.

It is well documented that in the presence of pulmonary hypertension, secondary to increased pulmonary vascular resistance, the murmur loses its pansystolic character.[2] Less well recognized is the fact that the murmur of a small ventricular septal defect may also greatly differ from the typical pattern.

In fact a pansystolic, plateau-shaped murmur was found in only half (11 out of 21) of the patients of the present study. Seven individuals had a distinct diamond-shaped murmur and in the remaining three children a short, early systolic, decrescendo murmur was found.

A gradient across the right ventricular infundibulum was not the only factor responsible for the production of a diamond-shaped murmur, for two patients without a demonstrable gradient had a diamond-shaped murmur, whereas four with a slight gradient had a plateau-shaped murmur. The latter observation may result because the pansystolic murmur of the ventricular septal defect masks the simultaneous and perhaps softer diamond-shaped murmur of very mild infundibular pulmonic stenosis. The diamond-shaped murmur of pure ventricular septal defect, on the other hand, may occur because turbulence created by a small orifice may be similar to that originating at the site of a stenosed pulmonary valve, and may reach its maximum intensity in midsystole. One of these diamond-shaped murmurs had a late systolic peak (fig. 4), which according to Vogelpoel and Schrire[10] is characteristic of severe pulmonic stenosis. The latter diagnosis could easily be disproved, however, even on physical examination, by the normally split second sound. These findings indicate that a sharp separation of "regurgitant" from "ejection" type systolic murmur[11] is not always possible. Even the most careful auscultation may fail to differentiate between a small ventricular septal defect, a ventricular septal defect with a slight degree of infundibular stenosis, and the rare case of isolated mild infundibular pulmonic stenosis.

Two of three patients with an early systolic decrescendo murmur had a minimal left-to-right shunt not demonstrable by oxygen saturation data. Although the presence of

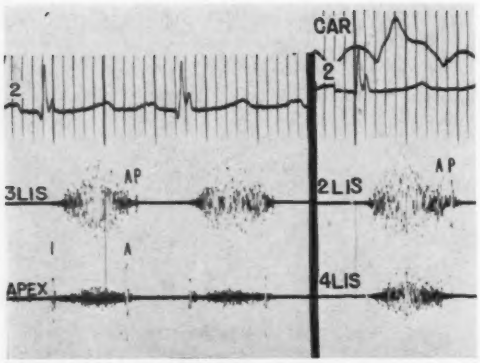

Figure 6

Diamond-shaped murmur with midsystolic peak in a patient with small shunt at ventricular level (Qp/Qs = 1.6) and an 8-mm. Hg infundibular gradient. The splitting of the second sound measures 0.04 second.

such a murmur certainly suggests a minimal defect, the fact that the third patient did show an appreciable increase in oxygen saturation (Qp/Qs = 1.7) indicates that this is not invariably the case. A plausible explanation of the pattern of this murmur may be that it originates from a small defect in the muscular portion of the ventricular septum closing off during systole. The same murmur was described by Evans et al.,[12] and a similar explanation was offered. The difficulty of separating this type of short and early systolic murmur from a so-called "innocent" or "functional" murmur is obvious. Even heart catheterization, if unaccompanied by more refined methods of shunt detection, may fail to reveal the true nature of the underlying abnormality. Thus the entire concept of what constitutes a "functional" murmur at the lower left sternal border may be brought under closer scrutiny, in terms of the criteria on which this diagnosis is based. Only one child had a mitral diastolic flow murmur, which contrasts with its common occurrence in larger ventricular septal defects.

In accordance with previous observations[1, 2] appreciable splitting of the second sound and inspiratory widening were recorded in all patients in whom a satisfactory tracing was obtained. Wide splitting was found in half of our cases, particularly in those with an associated slight infundibular gradient. In the latter group one could assume that the contraction of the infundibular chamber was prolonged as suggested by Johnson.[13] Wide splitting was also noted, however, in four patients without a gradient across the infundibular, suggesting that this may be inherent in the physiology of small ventricular septal defects and may be caused by prolongation of right ventricular systole itself. A hypothesis to explain this phenomenon may be offered. In contrast to the hemodynamics of large ventricular septal defects in which both ventricles act as a common ejectile force with the left ventricle directing blood into the pulmonary artery, in cases with a small opening in the ventricular septum, the left ventricle injects blood into the right ventricle, which in its turn forwards it to the pulmonary artery. Another hypothesis proposed for the wide splitting of the second sound in ventricular septal defect is based on the assumption that aortic closure occurs earlier than normal because of a shortened left ventricular systole.[4] Possibly a combination of these two mechanisms may cause the wide splitting of the second sound in these cases.

Summary

The auscultatory and phonocardiographic findings were analyzed in 21 cases of small ventricular septal defect. Eleven patients had identical right ventricular and pulmonary artery systolic pressures, whereas in nine a minimal systolic gradient across the infundibulum of the right ventricle was demonstrated. One half of the patients, with or without an infundibular gradient, had a pansystolic plateau-shaped murmur. Several patients, mostly those with an infundibular gradient, had a distinct diamond-shaped murmur. A few children showed an early systolic decrescendo murmur. Appreciable, even wide splitting of the second sound with inspiratory widening, was demonstrated. It is proposed that a sharp differentation between "ejection" and "regurgitant" systolic murmurs

may be difficult under certain circumstances. Furthermore, it is suggested that the definition of an "innocent" or "functional" murmur may depend on the sensitivity of the diagnostic methods used.

Acknowledgment

We should like to thank Drs. Abraham M. Rudolph and Anna J. Hauck for their help with the cardiac catheterization.

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Religio Medici

Nature a Bible Open to All

Thus there are two Books from whence I collect my Divinity; besides that written one of GOD, another of His servant Nature, that universal and publick Manuscript, that lies expans'd unto the Eyes of all: those that never saw Him in the one, have discovered Him in the other.—Sir Thomas Browne. *Religio Medici*, 1642. Edited by W. A. Greenhill, M.D., Oxon., London, MacMillan and Co., Limited, 1950, p. 27.

Relationship between Arterial Pressure and Exertional Angina Pectoris in Hypertensive Patients

By A. J. GEORGOPOULOS, M.D., F. M. SONES, JR., M.D., AND IRVINE H. PAGE, M.D.

ELEVATION of arterial pressure has been found in patients during attacks of angina pectoris[1-3] and relief of exertional angina has been reported in hypertensive patients following satisfactory control of hypertension.[4, 5] Further, anginal pain has been found to occur in hypertensive patients during lowering of arterial pressure.[4]

Although these observations suggest an etiologic correlation between angina pectoris and level of arterial pressure, this has not been adequately established. The present study was undertaken to determine the possible relationship between arterial pressure and exertional angina pectoris in hypertensive patients with and without coronary arterial disease.

Methods

Seven hypertensive patients (four women and three men) in the Research Ward of the Cleveland Clinic Hospital with unequivocal history of exertional angina pectoris of the functional class II were studied. Coronary arteriography by Sones' technic;[6] revealed segmental disease of the left coronary artery in four and of both coronary arteries in one (fig. 1); the remaining two were found to have normal coronary arteries (fig. 2).

Radiographic, as well as electrocardiographic, evidence of left ventricular hypertrophy was present in all. None had a history or electrocardiographic evidence of recent or remote myocardial infarction.

The five patients with coronary arterial disease had not taken any antihypertensive treatment prior to the study and during the study had moderate to severe hypertension; the two patients with normal coronary arteries had received guanethidine and had normal supine arterial pressure and significant postural hypotension.

Exercise was performed in sitting position on a stationary bicycle and in supine position by successive elevation of the legs with attached three-pound sand bags on each lower leg. The duration of exercise lasted 3 minutes, unless angina pectoris occurred earlier. The five patients with coronary arterial disease were subjected, in addition, to exercise in supine position during intravenous administration of sodium nitroprusside, as recommended by Page et al.;[7] in two of these, exercise was repeated 2 months after satisfactory control of hypertension was achieved with oral guanethidine.

Twelve-lead electrocardiograms (six standard limb leads and precordial leads V_1 through V_6) were taken prior to each exercise, and every 3 minutes thereafter three standard limb leads (I, II, III) and one precordial lead (V_5 or V_6) were taken for the following 15 to 20 minutes. The arterial pressure was measured sphygmomanometrically before exercise and every half minute during and following exercise.

In the two patients with normal coronary arteries, the effects of intravenous sodium nitroprusside (100 μg. per minute) and norepinephrine (5 μg.) given in the supine position were studied separately.

Results

Effects of Exercise on Five Patients with Angina Pectoris and Coronary Arterial Disease

During exercise, all five patients developed marked pressor response; the average increasing from 184/109 to 243/142 mm. Hg with exercise in supine position and from 179/110 to 216/120 mm. Hg with exercise in sitting position. Following exercise, arterial pressure returned to pre-exercise level within 3 minutes. Angina pectoris occurred in all, immediately after the peak of pressor effect was reached, within 1½ to 3 minutes from the beginning of the exercise and lasted from ½ to 1 minute. Because of anginal pain, exercise was discontinued earlier than had been planned in four.

From the Research Division and the Department of Cardiology of the Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute.

Presented at the Thirty-third Scientific Sessions of the American Heart Association, Saint Louis, Missouri, October 1960.

Dr. Georgopoulos' present address is 54 Hermou Street, Salonika, Greece.

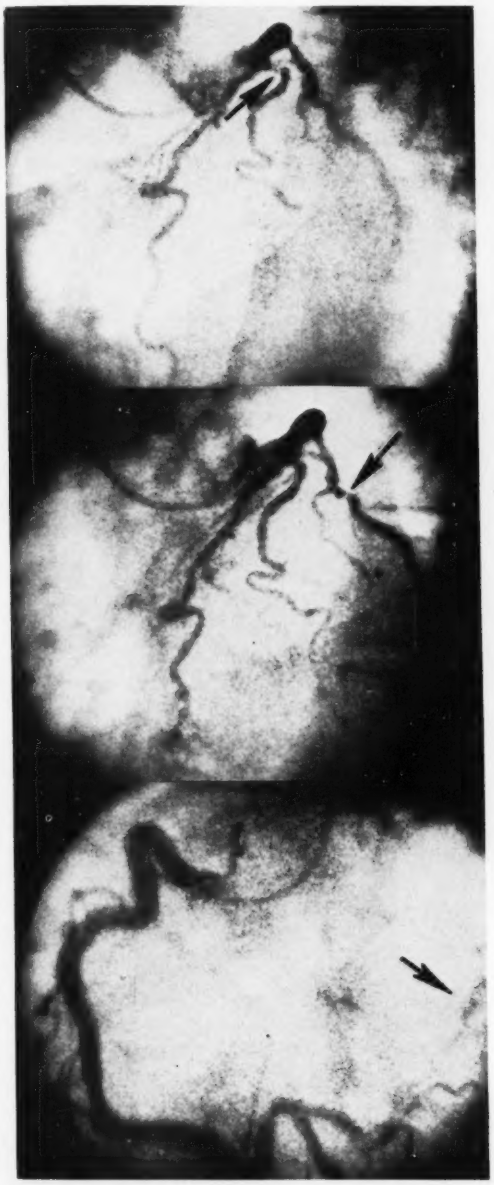

Figure 1

Coronary arteriograms on a 51-year-old man with hypertension and angina pectoris. Top. *Arrow points to a segmental lesion in a branch of the left anterior descending coronary artery. Patient is rotated in left anterior oblique position about 45 degrees.* Middle. *Another segmental lesion at the proximal third of the left circumflex coronary artery. Rotation of patient only slightly different from that in top figure. In top and middle figures the tip of the catheter is placed in the orifice of the main left coronary artery.* Bottom. *Normal right coronary artery. Arrow points to a collateral branch leading toward the distribution of the left circumflex coronary artery. Patient is rotated in left anterior oblique position about 60 degrees. Tip of catheter is placed in the orifice of the right coronary artery.*

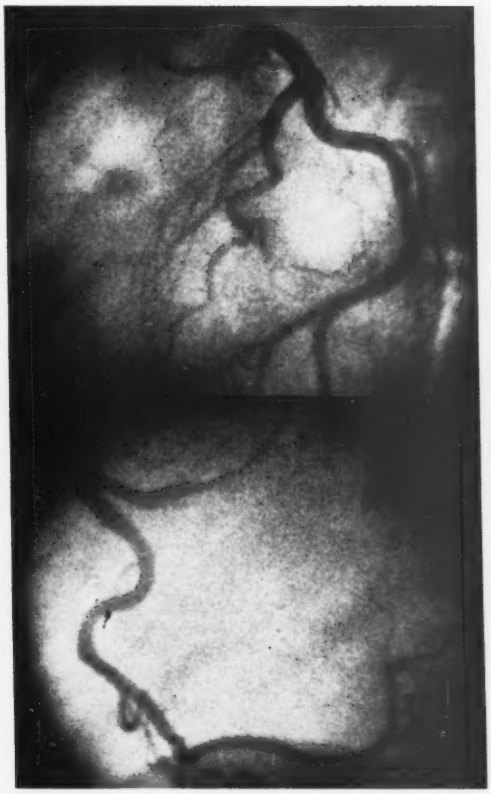

Figure 2

Normal left (top) *and right* (bottom) *coronary arteries. Catheter tip lies in the orifice of each artery. Patient is rotated in left anterior oblique position.*

Abnormal electrocardiographic responses were obtained in all, following exercise in both positions; these consisted of depressed S-T segments ranging from 1 to 2 mm. and inverted or diphasic T waves in one or more leads (figs. 3A and 4A); the changes lasted from 6 to 12 minutes and subsided gradually. In one, negative U waves appeared in lead

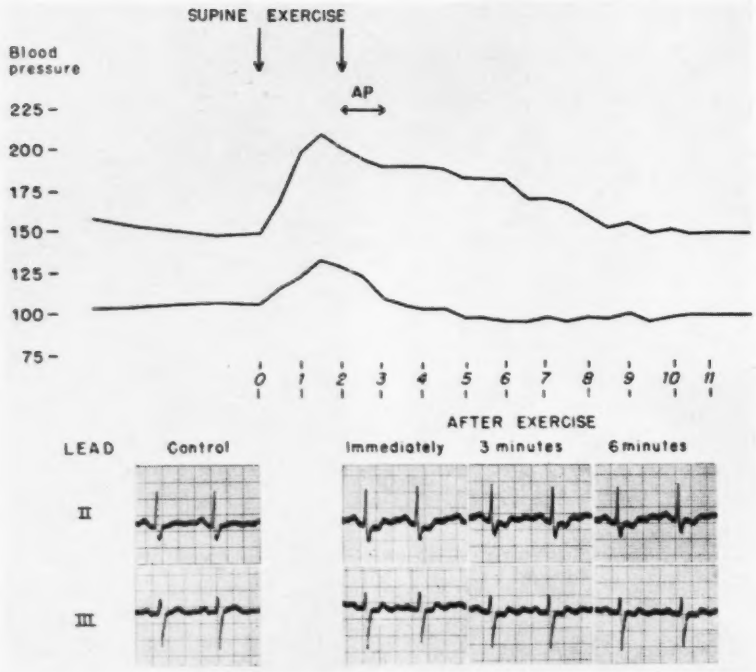

Figure 3A

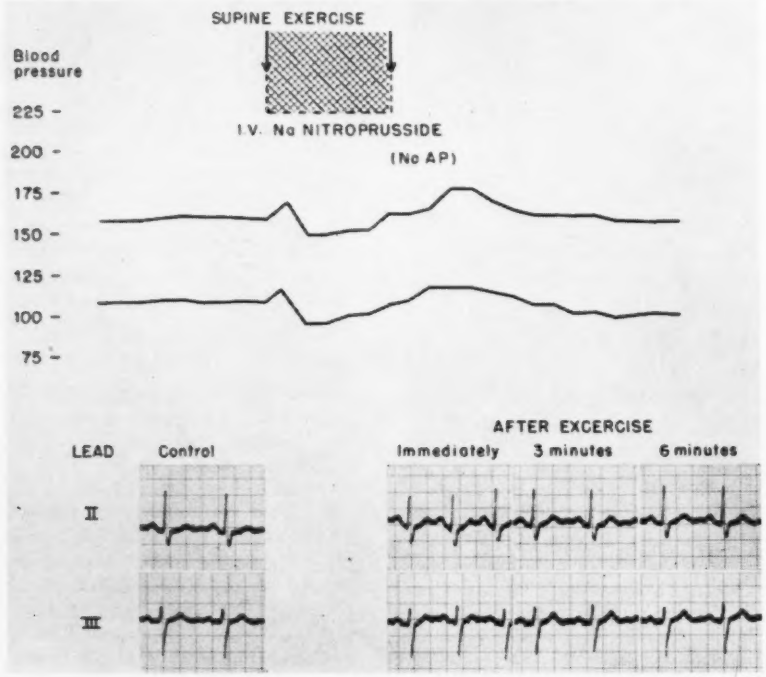

Figure 3B

V_5 immediately after exercise and became upright within 3 minutes, when the arterial pressure returned to control levels. Average increase in pulse rate when the angina pectoris occurred was 20 per minute. The pressor effect produced by exercise in the supine position was more pronounced than that in the sitting position; similarly, electrocardiographic changes, severity of angina pectoris, and the duration of both were greater with exercise in the supine position.

Effects of Exercise during Intravenous Administration of Sodium Nitroprusside on the Five Patients with Coronary Arterial Disease

With simultaneous intravenous infusion of sodium nitroprusside (400 to 600 μg. per minute) during the 3-minute exercise in supine position, pressor response to exercise was abolished in all; none experienced angina pectoris during or following exercise. Electrocardiographic changes did not occur (figs. 3B and 4B). Average pulse rate increased by 23 per minute over the pre-exercise control.

The results were reproduced in all patients in similar fashion on two occasions.

Effects of Exercise on Two Patients with Angina Pectoris and Normal Coronary Arteries

Both patients had orthostatic hypotension, secondary to antihypertensive treatment, which was exaggerated by exertion. A marked depressor effect occurred during exercise in the sitting position in both; average pressure fell from 122/86 to 80/55 mm. Hg. Angina pectoris developed immediately after the maximum depressor effect, about 2 minutes from the beginning of exercise, and lasted from ½ to 1 minute. Electrocardiographic changes (depressed S-T segments and diphasic T waves) appeared in both; these lasted from 6 to 9 minutes and gradually disappeared. In one, the depression of S-T segments was very pronounced (fig. 5A).

During exercise in supine position only minimal pressure changes occurred in both; angina pectoris and electrocardiographic changes did not occur (fig. 5B).

Additional Studies

Two of the five patients with coronary arterial disease, in addition, were subjected to 3-minute exercise in both positions, 2 months after control of hypertension with oral guanethidine. Exercise elicited no pressor response, no angina, nor electrocardiographic changes (fig. 4C).

In the two patients with normal coronary arteries, the effects of intravenous sodium nitroprusside (100 μg. per minute) and norepinephrine (5 μg.) in the resting supine position were studied separately. With sodium nitroprusside, arterial pressure was lowered to the same levels as with exercise in the sitting position during which angina pectoris had occurred before; with the norepinephrine the arterial pressure rose from 140/90 to 200/110 mm. Hg in one, and from 130/80 to 210/100 mm. Hg in the other. Neither the depressor nor the pressor effects produced angina pectoris or electrocardiographic changes.

Discussion

Rise in arterial pressure occurs in both normotensive and hypertensive patients during attacks of angina pectoris.[1, 2] We found that this elevation of arterial pressure in hypertensive patients with coronary arterial disease is an important precipitating factor in production of exertional angina pectoris. When the pressor response to exercise is eliminated by administration of an infusion of sodium nitroprusside or following antihypertensive treatment with guanethidine, angina pectoris, S-T depression and T-wave inversion can be prevented.

The mechanism by which elimination of the

Figure 3

A 39-year-old woman with hypertension, angina pectoris, and coronary arterial disease. A. Marked pressor response to exercise occurred; this was followed by angina pectoris and electrocardiographic changes. Numbers below arterial pressure graph indicate time in minutes. B. Marked pressure changes were not produced by a 3-minute exercise in supine position during intravenous sodium nitroprusside administration. Angina pectoris and electrocardiographic changes did not occur.

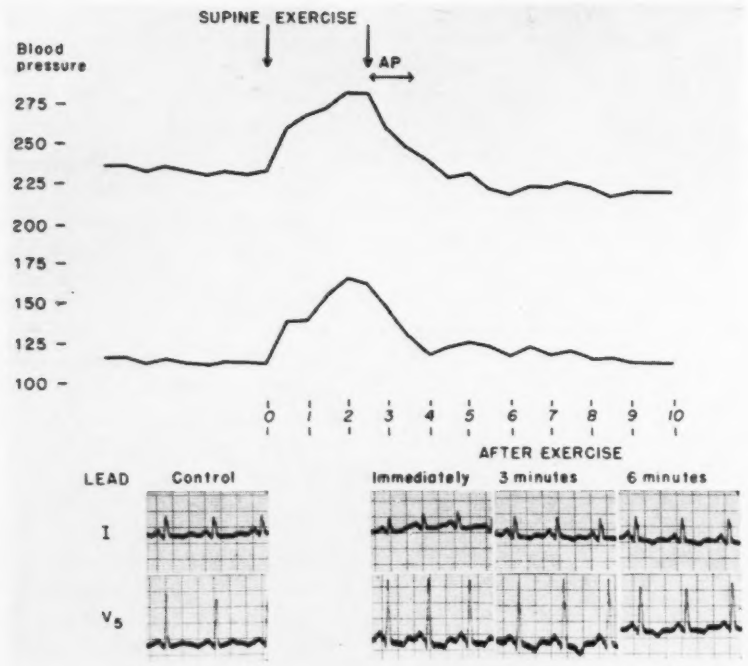

Figure 4A

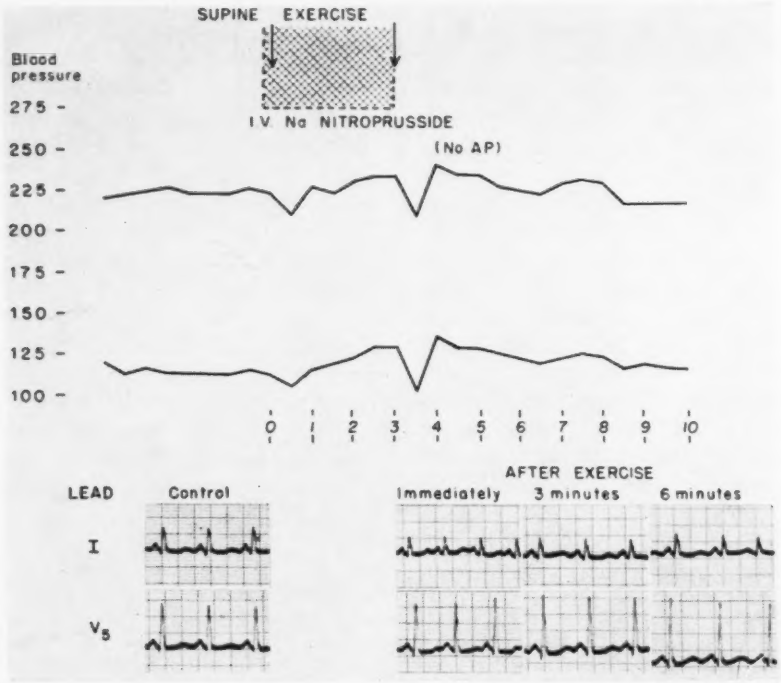

Figure 4B

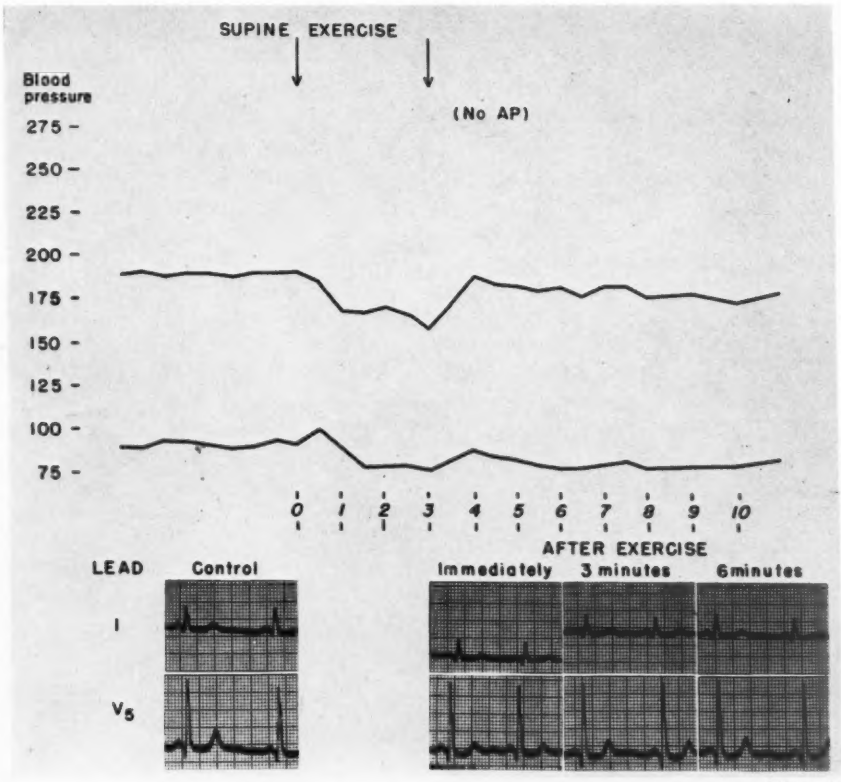

Figure 4

A 59-year-old man with severe hypertension, angina pectoris, and segmental disease of both coronary arteries. A. Exercise prior to treatment with guanethidine. Marked pressor response occurred, followed by angina pectoris and electrocardiographic changes. B. Similar exercise as in A (the same day). Intravenous sodium nitroprusside during exercise eliminated the pressor response and prevented angina pectoris and electrocardiographic changes. C. Supine exercise after 2 months' treatment with oral guanethidine. Marked arterial pressure changes, angina pectoris, and electrocardiographic abnormalities did not occur.

pressor effect of exercise inhibits induction of angina pectoris is not clear. Arterial pressure is one of the most important constituents of the work of the heart, and angina pectoris may be relieved by decreasing cardiac work. It is therefore probable that in hypertensive patients reduction of cardiac work by eliminating the pressor effect of exercise is a significant factor in preventing attacks of exertional angina pectoris.

Tachycardia occurring during exercise has been suggested as a possible cause of exertional angina pectoris.[2] In our study, increase in heart rate was not an important factor because it also occurred when the angina pectoris was prevented with administration of sodium nitroprusside.

The possibility of a direct action of sodium nitroprusside on the coronary arterial circulation has not been completely eliminated. In two patients in whom we had the opportunity to perform coronary arteriography before and after intravenous administration of sodium nitroprusside, we did not observe dilatation of coronary arteries similar to that seen in patients following administration of nitro-

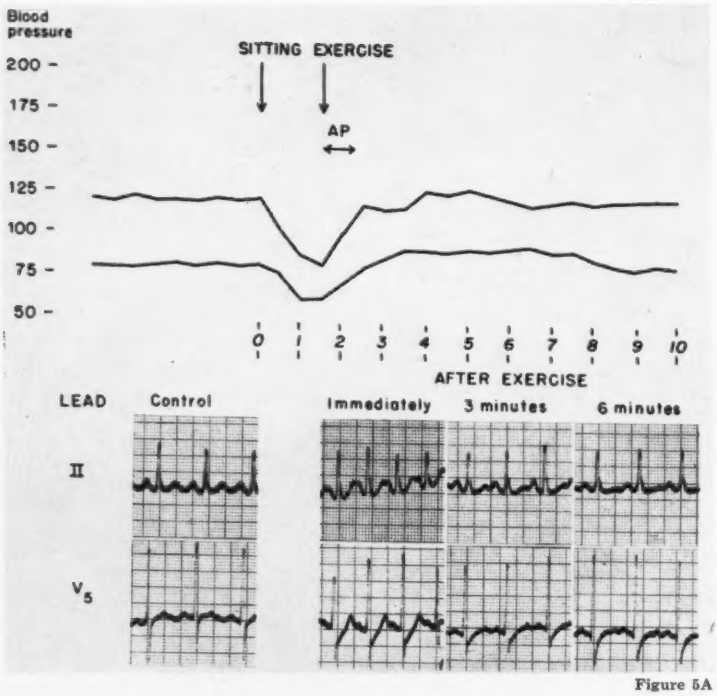

Figure 5A

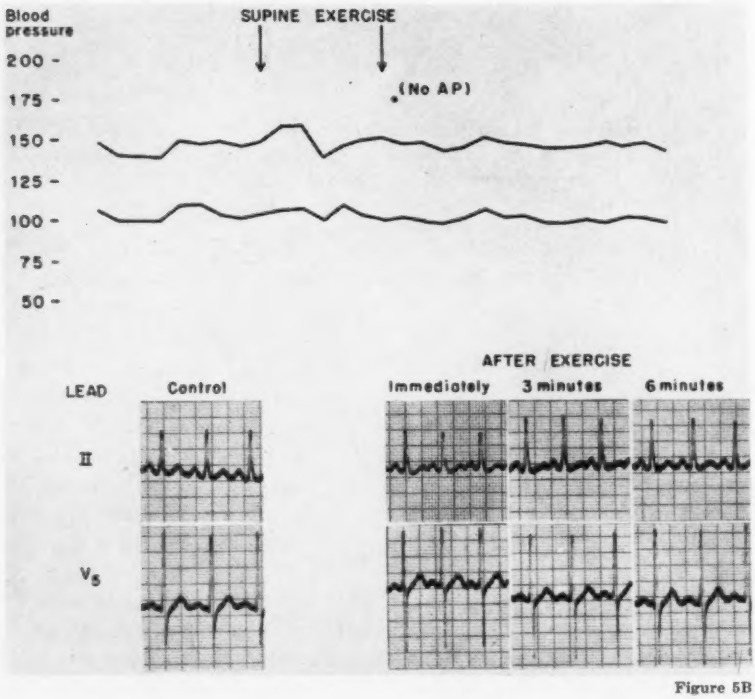

Figure 5B

glycerin.[8] Since angina pectoris also did not occur with exercise in the two patients treated with guanethidine, we assume that sodium nitroprusside relieved angina pectoris, not by a direct vasodilating effect on the coronary arteries, but by eliminating the pressor response to exercise.

The occurrence of angina pectoris in the absence of obstructive lesions in the coronary arterial tree has been reported in severe anemia,[9] aortic valve lesions,[10] and patients with hypertension.[11] We found that marked temporary fall in arterial pressure is a factor of importance in precipitating exertional angina pectoris in hypertensive patients. The two patients in whom this occurred had left ventricular hypertrophy and normal coronary arteries. Since it is known from the work of Roberts and Wearn[12] that the capillary bed of the hypertrophied myocardium is decreased in proportion to the increase in heart weight, we assume that the fall in arterial pressure results in a further reduction in the myocardial blood supply, leading to exertional angina pectoris. Because angina was not produced in these two patients by exercise in the supine position, during which fall in arterial pressure was avoided, we conclude that hypotension was the main factor in the production of exertional angina pectoris.

The possibility exists that hypertensive patients with coronary arterial disease may also experience angina as a result of lowered arterial pressure during exercise. Similarly, in hypertensive patients with normal coronary arteries and angina,[11] elevation of arterial pressure during exercise may be an important factor in precipitating angina pectoris. Both these two possibilities, not studied here, would need further investigation.

Summary

Seven hypertensive patients, five with coronary arterial disease and two with normal coronary arteries, with exertional angina pectoris and left ventricular hypertrophy were subjected to exercise in the sitting and supine position.

The five patients with coronary arterial disease developed, during exercise in both positions, striking arterial pressure elevation followed by angina pectoris and electrocardiographic changes. When the pressor response to exercise was eliminated by intravenous sodium nitroprusside, these were prevented.

In the two patients with normal coronary arteries who had orthostatic and exertional hypotension secondary to antihypertensive treatment, exercise in the sitting position caused intense hypotension followed by angina pectoris and electrocardiographic changes. In contrast, exercise in the supine position, which caused only minimal pressure changes, was not followed by angina pectoris.

It is concluded that in hypertensive patients with coronary arterial disease, further elevation of arterial pressure during exercise is an important factor in precipitating angina pectoris by increasing cardiac work. In hypertensive patients with normal coronary arteries and exertional hypotension secondary to antihypertensive treatment, marked lowering of arterial pressure during exercise is a factor of importance in producing angina pectoris, probably by reduction of perfusion pressure and coronary flow relative to the hypertrophied left ventricle.

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Figure 5

A 35-year-old hypertensive woman with exertional hypotension, angina pectoris, and normal coronary arteries. A. *Sitting exercise produced marked depressor response, angina pectoris, and pronounced depression of the S-T segments in lead V_5 of the electrocardiogram.* B. *Three-minute exercise in supine position did not produce pressure changes, angina pectoris, or electrocardiographic abnormalities.*

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The great and fruitful ideas which Darwin brought to the attention of the whole world have long since been incorporated into human thought. Not the least important among them is the new scientific concept of fitness, as it emerges from the discussion of natural selection. Before Darwin, this concept possessed all the vagueness of an idea which, though in part founded on observation, was not to be explained with the help of existing scientific theories. But although Darwin's fitness involves that which fits and that which is fitted, or more correctly a reciprocal relationship, it has been the habit of biologists since Darwin to consider only the adaptations of the living organism to the environment. For them, in fact, the environment, in its past, present, and future, has been an independent variable. Yet fitness there must be, in environment as well as in the organism. How, for example, could man adapt his civilization to water power if no water power existed within his reach?—LAWRENCE J. HENDERSON. *The Fitness of the Environment.* New York, The MacMillan Co., 1924 p. 5.

Prediction of Fainting in Blood Donors

By DAVID T. GRAHAM, M.D.

IT SEEMS PROBABLE that almost all of the so-called "reactions" in blood donors are partial or complete vasovagal faints. In a study of fainting, data were obtained from 414 consecutive blood donors before the drawing of blood was begun. It was hoped that some of the routine, easily obtained data from such persons would permit selection of donors who were likely to faint.

The major hypothesis under investigation is that vasovagal fainting is the second limb of a diphasic response. The first limb is characterized by increases in heart rate and blood pressure. If these phases occur as an emotional response, the first is part of anxiety, defined as the response to a threat, but the second is part of sudden relief from anxiety. The change from the first to the second phase occurs when the person sees himself as no longer threatened, either because danger has safely passed or because a threat has actually been carried out.

The hypothesis also suggested that cardiovascular indications of anxiety would be more prominent in those donors who subsequently fainted, than in those who did not. Systolic and diastolic blood pressure and pulse rate were routinely obtained in all prospective donors as part of the ordinary operation of the blood-donor room. Further, each prospective donor was asked whether or not he felt "nervous." This word was thought to be in actual usage nearly synonymous with "anxious," which many donors would not have understood. This was the only item of information that had to be especially gathered for this research. Data on race, age, sex, and previous blood donations were included in the study because they were obtained as part of the ordinary routine for blood donation.

From the Department of Medicine, University of Wisconsin, Madison, Wisconsin.

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Read before the Meeting of the American Association of Blood Banks, Chicago, Illinois, November 5, 1957.

Subjects

The subjects of the study were 414 blood donors at a hospital blood bank. These were consecutive, except for the exclusion of 81 for whom some information (usually the item about "nervousness") was missing from the record before donation. During the course of the study 495 donors actually were bled. Most of the donors had come in response to a request from the hospital to replace blood received by friends or relatives. A few were professional donors; data concerning them were not handled separately.

Procedure

The data were gathered by technicians regularly employed in the blood bank as well as by medical students who had part-time jobs there. No change was made in the existing system of recording information on separate cards for each donor, except that an additional note for the question about "nervousness" had to be made, which was no doubt the reason for its frequent omission.

At the conclusion of the donation, a note was made on a card if the donor had had a reaction. The definition of "reaction" used in this study was simply the presence of symptoms or signs of generalized discomfort (thus excluding pain at the venipuncture site, for instance) of sufficient severity that the donor either called them to the attention of the staff or that they were observed by the staff. They consisted chiefly of pallor, sweating, and disturbance of consciousness ranging from slight "lightheadedness" to complete unconsciousness. It is true that this definition may have caught a few examples of reactions other than vasovagal faints, but it is thought that these exceptions were few. The usual procedure for donors involved a wait of from 1 to 30 minutes outside the room in which the blood was actually drawn, during which time they checked off on their cards a list of symptoms or illnesses that might disqualify them. During this wait blood was obtained by a finger puncture for a rapid estimation of hemoglobin content. The donor then

Table 1

*Relation of Variables Studied to Fainting Rate**

		% Fainted	Correlation with fainting	Statistical measure and value	Significance
Race	Negro	0.0		$\chi^2 = 11.74$	$p < .01$
	White	17.9			
Sex	Men	17.8		$\chi^2 < 1.0$	Not significant
	Women	18.5			
"Nervousness"	"Nervous"	28.6		$\chi^2 = 6.65$	$p < .01$
	Not "nervous"	12.9			
Donation history	First-time	22.4		$\chi^2 < 1.0$	Not significant
	Repeaters	16.5			
Age			Negative	$r_{bis} = -0.286$	$p < .01$
Pulse rate before donation			Positive	$r_{bis} = 0.243$	$p < .01$
Blood pressure before donation	Systolic		No correlation	$r_{bis} = 0.005$	Not significant
	Diastolic			$r_{bis} = -0.0007$	Not significant
	Pulse			$r_{bis} = -0.001$	Not significant
	Mean			$r_{bis} = 0.06$	Not significant

*Except for race, all comparisons apply to white donors only.

lay down on an examining table and his pulse rate and blood pressure were determined.

Prospective donors were occasionally rejected before this point was reached because they gave a history of a disqualifying symptom or illness. In addition to a negative history in this respect, the major relevant criteria for acceptance were age between 18 and 60 inclusive, weight greater than 110 pounds, oral temperature 99.6 F. or less, pulse rate between 60 and 100 inclusive, systolic blood pressure between 100 and 200 mm. Hg, and diastolic less than 100 mm. Hg. Minor deviations from the pulse and blood pressure criteria were permitted at the discretion of a physician in attendance, especially if a few minutes' rest brought them within the acceptable range.

If the donor was acceptable, a tourniquet was placed around one arm, and a needle was inserted into the antecubital vein. The blood flowed into a collecting bag, which was out of his normal line of sight, but which he could see if he made an effort to do so. Approximately 520 ml. were withdrawn.

The time spent in the various stages of the process varied a good deal from donor to donor, depending on how taxed the staff and facilities were. The time actually required to collect the blood after the needle was inserted varied from about 6 to 15 or 20 minutes.

When collection had been completed, the donor was allowed to sit up if he felt well, was given milk or fruit juice to drink, and was then asked to sit for about 5 minutes outside the room to make sure no reaction would develop. A reaction occurring at any time was included in the final tabulation.

Results

All the reactions reported are referred to as "faints": 15.2 per cent of all donors fainted.

Race. None of the 62 Negro donors fainted, whereas 17.9 per cent of the 352 white donors fainted, a statistically significant difference (table 1). Since no faints occurred among the Negroes, this group is not included in analyses of the remaining data. All subsequent findings refer to the white donors only.

Sex. There were 54 women and 298 men among the white donors: 18.5 per cent of the women and 17.8 per cent of the men fainted. There was not a significant difference in fainting between the two sexes (table 1).

Age. There was a definite association between age and the occurrence of fainting: the younger the donor, the more likely was he to faint (table 2).

"Nervousness." "Nervousness" was admitted by 31.8 per cent of the white donors: 28.6 per cent of these "nervous" donors fainted. Of the remaining 68.2 per cent who denied "nervousness," 12.9 per cent fainted. A donor who admitted to anxiety was, there-

Table 2

White Donors' Frequency of Fainting According to Age

Age	Proportion fainted
50-59	0/21 = 0%
40-49	8/79 = 10%
30-39	24/125 = 19%
20-29	28/117 = 24%
10-19	3/10 = 30%

Table 3

White Donors' Frequency of Fainting According to Initial Pulse Rate

Pulse rate	Proportion fainted
≥ 100	15/35 = 43%
90-99	15/73 = 21%
80-89	21/155 = 14%
70-79	8/72 = 11%
60-69	4/17 = 24%

fore, more than twice as likely to faint as one who denied it.

Pulse Rate. The pulse rate before donation also proved to be significantly related to subsequent fainting. Except for the very slow rates, the higher the pulse rate, the more likely was a faint to occur (table 3).

Blood Pressure. The blood pressure measurements are certainly not very accurate; there are, for instance, far too many readings in multiples of 10. Nevertheless, if an important relation between pressures and fainting existed, it would have been expected to appear. Neither systolic, diastolic, nor pulse pressure obtained before the blood donation was found to be correlated with subsequent occurrence of fainting. Mean blood pressure, estimated by the formula $\text{DBP} + \frac{\text{SBP-DBP}}{3}$, also did not correlate with subsequent fainting (table 1).

Previous Donation. Eighty-five of the subjects gave blood for the first time; 267 had made previous donations. The difference in fainting between the two groups was not significant (table 1).

Relations among Items. The significant predictors of fainting are by no means completely independent of each other. Actual intercorrelations were not computed, but inspection of the data showed that "nervousness," youth, and high pulse rates tended to be present in the same donors.

On the other hand, there was enough independence so that, by combining the significant items, it was possible to define donor groups with very high probabilities of fainting (table 4). Naturally, the larger the number of faint-predictors required in a single person, the smaller is the group containing only such persons. There were, for example, only seven who were white, under 30, "nervous," and with pulse rates of 100 or more, but five of these fainted, a rate of 71.4 per cent.

Discussion

The number of donors studied here is small compared to some of the groups reported by others. The data appear to be meaningful, however, since the statistical evaluation of significance takes account of the size of the group.

A correlation between high pulse rates before blood donation, and vasovagal fainting later was obtained. There was no evidence of correlation between elevated blood pressure, as routinely determined before donation, and subsequent low blood pressure. Brown and McCormack[1] mention that "high blood pressure and high pulse rate were often seen before bleeding" in donors who later fainted, but they did not investigate this relation systematically.

The relatively high frequency of faints in donors with the lowest initial pulse rates, even though the total number in this group is small, runs counter to the trend in the rest of the subjects. A suggested explanation is that some of these donors had in fact already "begun to faint," so to speak, and that the low pulse rate reflects this fact. If this is true, the event that precipitated this kind of "partial faint" may have been the puncturing of the finger for the hemoglobin estimation. This seemed to be a threat of some importance to some very anxious per-

Table 4

Combinations of Factors White Donors

Age <30,	Pulse ≥ 90,	Not "nervous"	16/46 = 35% Fainted
Age <30,	Pulse ≥ 90,	"Nervous"	11/23 = 48% Fainted
Age <30,	Pulse ≥ 100,	Not "nervous"	6/12 = 50% Fainted
Age <30,	Pulse ≥ 100,	"Nervous"	5/7 = 71% Fainted

sons, and, in fact, on rare occasions fainting is seen after it.

The over-all incidence of fainting in this study is surprisingly larger than that reported by others. No incidence greater than 7 per cent was found.[1-6] It is not easy to be sure to what extent the groups of donors are comparable. The references cited above deal with blood-collection efforts in connection with war-time needs. A great many of the present donors were giving blood because close friends or relatives were seriously hurt or ill, and it seems likely that their anxiety about the blood-drawing itself might have been superimposed on a high level of anxiety already present for other reasons. It is also possible that in the present work milder reactions were counted than was true in other investigations, and also that there was more opportunity for close individual attention to donors and hence for observing reactions that might otherwise have passed unnoticed.

No mention has been found of low incidence of vasovagal fainting in general, or of blood donation "reactions" in particular, in Negroes. Reactions in Negro donors are sometimes seen in the blood-donor room where the present data were gathered, but the rate must be substantially lower than that for white subjects.

There is no obvious explanation of the racial difference found. Statistical evaluation showed no significant differences between the means of the two groups in age, initial pulse rate, systolic blood pressure, or mean blood pressure; or between the groups in sex distribution or admission of "nervousness." The Negro donors' mean diastolic pressure was 81 mm. Hg as opposed to the whites' 77. This difference is statistically significant ($p<.01$), but its meaning is doubtful in view of the lack of correlation between blood pressure and fainting in the white group. The Negroes' mean pulse pressure was 50 mm. Hg, the white persons' 53. The probability that this difference could arise by chance is less than 5 per cent, but, again, since there was no correlation in the white group between pulse pressure and fainting, it is doubtful that it helps to explain the racial difference in fainting. It is possible that the latter represents some kind of social or cultural artifact, having to do with the circumstances under which persons come to give blood. Certainly there seems no reason to think that anxiety is any less common in general among Negro than among white persons.

In other respects, in which the variables corresponded, the findings of the present study are generally concordant with those of others. Age has been four times previously reported to be negatively correlated with fainting in blood donors.[2-5] One report[6] denies such a relation. In it, however, the age groupings in handling the data are such that the correlation may be somewhat obscured; furthermore, its tables show that more fainting was in fact found in the youngest group than in the others.

There have been varied reports about the influence of sex on reaction rate in donors. One study[5] showed a higher rate for young men than for young women, with little difference in older subjects; two, a higher rate for women than men;[2, 6] and two[3, 4] concluded that there was no difference, which agrees with the present data. The explanation of these disparities probably lies in differences in donor populations in such things as equality of age between sexes and whether the men had been rejected for military service.

No other investigators seem to have at-

tempted an objective assessment of the incidence of "nervousness" in their donors. When the word is mentioned,[1, 3] it is not clear to what extent the evaluation is by an observer and to what extent by the donor himself. Presumably, no matter who uses it, it refers to what would more precisely be called "anxiety." The higher rate of fainting in donors who admitted "nervousness" than in those who did not is of some general interest, apart from its value in predicting the occurrence of fainting. It indicates that, at least in this limited setting, a conscious statement about emotional status has real meaning, since it is useful in making a prediction.

Two previous reports[4, 6] are in agreement with this one in finding a slightly higher risk of fainting in first-time donors, although, as in this one, the difference was not striking.

Various other possible factors influencing the fainting rate have been examined by others. These did not, in general, appear to be of much assistance in prediction. It is worth mentioning, however, that Poles and Boycott,[4] found a fainting rate of 8.5 per cent if 540 ml. of blood were removed, as opposed to 3.8 per cent if only 440 ml. were taken. One important piece of information is a history of previous fainting in any circumstances, which is mentioned in three reports[1, 3, 6] as valuable in differentiating fainters from nonfainters among blood donors. This was not investigated in the present study.

Since serious consequences of donor faints must be extremely rare, preventing them is probably not a matter of great importance. Yet it does seem desirable to keep the rate as low as possible, and the results of this and previous studies do suggest some steps to take. In the first place, it is possible to recognize the donors who are most likely to faint, and therefore to concentrate preventive measures where they will do the most good. In the second place, it seems likely that steps to reduce anxiety *before* the insertion of the needle are crucial, and that after this point the process may be difficult to alter. A number of obvious possibilities exist in terms of verbal and nonverbal reassurance, manipulation of the atmosphere and operation of the blood-donor room, and so forth. Williams[5] found that donors dealt with by inexperienced personnel had a fainting rate only about one third that of donors handled by experienced medical officers; he attributed this difference to the fact that the inexperienced persons were "constantly in personal touch with each donor."

Until actual experimentation is done, it is not possible to know what steps, if any, will reduce anxiety or the fainting rate, or both. Although studies like the present one show a correlation between indicators of anxiety and fainting, which are useful in prediction, they do not by themselves establish that fainting would not occur if the anxiety were reduced; it is theoretically possible (although not the author's opinion) that the anxiety and the subsequent fainting are not directly linked, but rather that they both reflect some third, unknown variable.

Summary

Four hundred and fourteen consecutive blood donors to a hospital blood bank were studied to discover items of value in predicting the occurrence of "reactions." Since it is probable that blood donor "reactions" are almost always vasovagal faints, they are so referred to below.

Several items of predictive value were found: none of the 62 Negroes, but 63 of the 352 white persons fainted; the younger the donor, the more likely a faint; the higher the resting pulse rate before venipuncture, the more likely a faint; admission of "nervousness" was associated with greater chance of fainting than was denial.

Sex, resting blood pressure before venipuncture, and history of previous blood donation did not significantly differentiate fainters from nonfainters.

The data are compatible with the hypothesis that vasovagal fainting in blood donors is the second limb of a diphasic response, and is part of relief from anxiety; the first limb is part of anxiety proper.

Acknowledgment

Thanks are expressed to Olivia J. Pautler for technical assistance.

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Then, to gain some idea of the quantity of air that was actually taken into the body during breathing, he constructed inspiratory and expiratory valves, and inspired a measured volume of air out of a container; at the same time he collected all his expired air over water (Plate IX, fig. A). On returning his expired air back into the container, he found that 1/136th of its original volume had disappeared.—A. E. Clark-Kennedy, M.D., M.R.C.P. *Stephen Hales, D.D., F.R.S.* Cambridge, University Press, 1929, p. 102.

The Surgical Therapy of Extracardiac Anomalous Pulmonary Drainage

By Roy R. Vetto, M.D., David H. Dillard, M.D., Thomas W. Jones, M.D., Loren C. Winterscheid, M.D., and K. Alvin Merendino, M.D.

THE PURPOSE of this paper is two-fold: first, to review the surgical experience of the past 10 years, with reference to the broad anatomic and physiologic classifications; and secondly, to present a series of 10 patients with *extracardiac* anomalous pulmonary venous drainage, treated surgically with the aid of extracorporeal circulation.

Prior to 1950 the only mode of surgical therapy available for anomalous pulmonary venous drainage was resection of the involved pulmonary tissue. The concept of direct repair of the abnormal drainage patterns has evolved during the past 10 years. Among pioneers in the development of this concept should be listed Muller,[1] who described the first successful partially corrective surgery for anomalous venous drainage in 1951; Burroughs and Kirklin[2] and Lewis and co-workers,[3] who described successful complete corrections of total anomalous pulmonary venous drainage in 1956; Cooley and Ochsner[4] (1957), who improved surgical technics; and Mustard and Dolan,[5] who in 1957 presented the first significantly large series of surgically treated cases.

Anomalous venous drainage may be divided anatomically into two large groups: (1) those that drain via extracardiac channels, i.e., via the coronary sinus, the right superior vena cava, persistent left anterior cardinal vein (persistent left superior vena cava), inferior vena cava, and portal vein; and (2) those that drain via intracardiac channels, namely, anomalous drainage into the right atrium. Physiologically, the defects may also be separated into two large categories: those with total and those with partial anomalous venous drainage.

A total of 21 articles dealing with surgical treatment for anomalous pulmonary venous drainage in 166 cases was found in the literature.[1-21] In absolute numbers, total anomalous pulmonary venous drainage via extracardiac channels in this series of operated patients was encountered more than four times as often as total anomalous pulmonary venous drainage via intracardiac channels (table 1). Only 20 case reports (12 per cent) were found in which extracorporeal circulation was utilized in the repair. Extracorporeal circulation was used more frequently in patients with total anomalous venous drainage via an extracardiac site. Survival rates for all cases and for the various groups under analysis are listed in table 2.

Several generalizations may be made. The survival rate with surgical treatment is significantly lower with total anomalous pulmonary venous drainage, and also when drainage is via extracardiac channels. Although the number of patients treated with extracorporeal circulation is small, the figures suggest that survival rates are generally better with this technic. This appears to be particularly true in cases of total anomalous drainage. The group of patients with total anomalous drainage via extracardiac channels appears to have the poorest surgical prognosis. Therefore, a more complete analysis of this group was made (table 3). Although extracardiac total anomalous pulmonary venous drainage via the inferior vena cava, portal vein, etc., has been reported, there was no report of surgical

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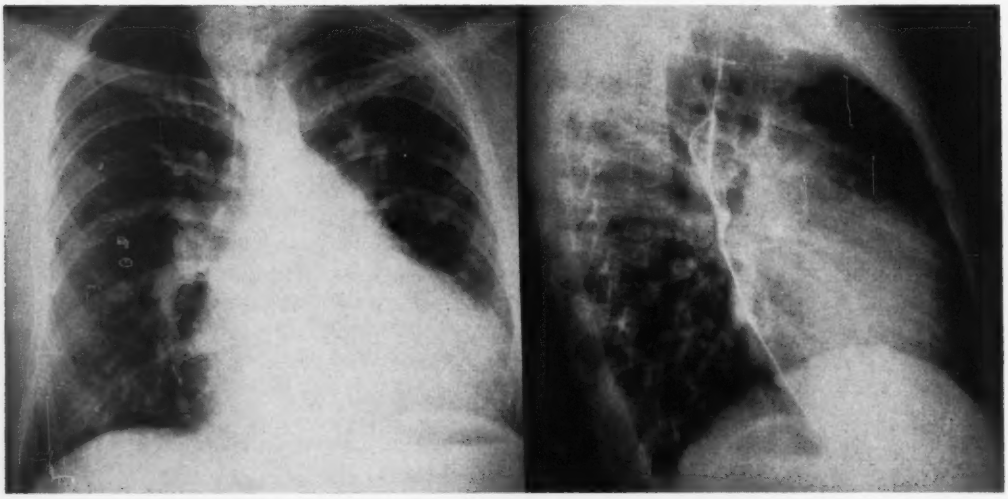

Figure 1

Posteroanterior and lateral x-rays of patient 6 (partial anomalous pulmonary venous drainage with large shunt and low pulmonary vascular resistance). The right atrium, right ventricle, and common pulmonary artery are enlarged, and peripheral pulmonary engorgement is evident.

correction of this anomaly. Consequently, the only reports available were on patients in whom the total anomalous drainage was into the superior vena cava, the coronary sinus, or a persistent left anterior cardinal vein. Fifty-three such cases were found, and in 34 drainage was via a persistent left anterior cardinal vein. The survival rate was lowest in this single category, whether or not pump-oxygenator support was used.

Survival per se is not, however, the ultimate goal in treatment of this type of patient. Though major degrees of improvement have been afforded by a partial correction of the anomaly, the surgical goal should be the complete correction of the anomaly. Table 4A documents the number of patients who have had a complete repair of total anomalous venous drainage accomplished with survival. Only nine of 53 patients survived with a complete correction (17 per cent). Again, the group with a persistent left anterior cardinal vein fared the worst of all, for only three of 34 patients (9 per cent) had a complete repair with survival. A greater percentage of patients with total anomalous venous drainage had complete correction with the aid of extracorporeal circulation (three out of 12, or 25 per cent), than patients operated upon without extracorporeal circulation (six of 41, or 15 per cent). Table 4B shows the number of patients in the *survivor* group of total anomalous venous drainage who received complete repairs. Nine of 24 surviving patients had complete repairs (37 per cent). Although relatively few had complete correction, no attempt at complete repair was made, in many instances in the interests of survival of a patient. Consequently, an effort was made to determine the survival rate of patients in those reports in which it was clearly stated that complete repair was attempted (table 5). In only 15 instances was it completely clear that the operator intended a complete repair; and there were nine survivals (60 per cent).

Authors' Series

Clinical Material

Our series consists of 10 patients with extracardiac anomalous pulmonary venous drainage, treated with extracorporeal circulation from August 1956 to January 1960. This

Table 1

All Cases of Anomalous Pulmonary Venous Drainage Treated Surgically from 1950-1960

Number of patients in combined series	166
Number of patients treated with aid of extracorporeal circulation	20 (12%)

		All patients		Patients treated with Aid of EC	
		No.	%	No.	%
Total APVD		65	39.1	16	80
Partial APVD		101	60.9	4	20
Extracardiac drainage		95	57	15	75
Intracardiac drainage		71	43	5	5
Extracardiac drainage	TAPVD	53	56	12	80
	PAPVD	42	44	3	20
Intracardiac drainage	TAPVD	12	17	4	80
	PAPVD	59	83	1	20

Abbreviations (apply for all charts and figures): APVD, anomalous pulmonary venous drainage; T, total; P, partial; EC, extracorporeal circulation; PLAC, persistent left anterior cardinal vein; CS, coronary sinus; S, survivals; SVC, superior vena cava.

Figure 2

Posteroanterior x-ray of patient 5 (partial anomalous pulmonary venous drainage, with small shunt and high pulmonary vascular resistance). Marked common pulmonary artery enlargement contrasts with "normal" peripheral lung fields.

represents 7 per cent of all patients operated upon with cardiac bypass by the University of Washington group during that time. All patients had an associated atrial septal defect. Of the 10, seven were male. Ages ranged from 3½ to 51 years (11 to 51 years with partial anomalous pulmonary venous drainage, and 3½ to 11 years with total anomalous pulmonary venous drainage).

Symptoms and Signs

As expected, the symptoms and signs varied in the two physiologic groupings. In patients with partial anomalous pulmonary venous drainage, symptoms and signs closely resembled those seen with atrial septal defects. Cardiac murmurs were usually discovered relatively early in life, though disability did not occur before the second decade. A pulmonary systolic murmur was ordinarily heard, and the pulmonary second sound was frequently accentuated and split.

In contrast, patients with total anomalous pulmonary venous drainage showed moderate to severe impairment of physical activity, and, in general, significant retardation of physical maturity. Murmurs were essentially the same, but more marked, as were clinical indications of right ventricular overwork. Most patients show perceptible oxygen desaturation at rest; those who do not, frequently develop desaturation during exercise. Stigmata of oxygen desaturation, e.g., clubbing, increased hematocrit value, etc., may be present.

Catheterization Data

The data of cardiac catheterization in these 10 patients are illustrated in table 6. In general, the shunts were large, and pulmonary vascular resistance was low. Two exceptions were patients nos. 4 and 5, aged 33 and 41, who had relatively small shunts and high resistances. Both patients had partial anomalous venous drainage. Three of four patients with total anomalous venous drainage had oxygen desaturation at rest. Nine of the 10 patients had some degree of right-sided hypertension, and most had a pressure gradient across the pulmonary valve, secondary to increased flow, rather than anatomic restriction. The exception was the first patient, who also had pulmonary valvular stenosis. Right

Table 2

Survival Rates

A. All patients

	Combined group			With EC			Without EC		
	No.	S	%	No.	S	%	No.	S	%
All cases	166	123	74	20	14	70	146	109	75
Total APVD	65	34	52	16	11	69	49	23	47
Partial APVD	101	89	88	4	3	75	97	86	89

B. Patients with intracardiac drainage

	Combined group			With EC			Without EC		
	No.	S	%	No.	S	%	No.	S	%
All cases	81	72	89	5	5	100	54	39	72
Total APVD	12	10	83	4	4	100	8	6	75
Partial APVD	47*	34	72	1	1	100	46	33	72

C. Patients with extracardiac drainage

	Combined group			With EC			Without EC		
	No.	S	%	No.	S	%	No.	S	%
All cases	85	51	60	15	9	60	70	42	60
Total APVD	53	24	45	12	7	58	41	17	41
Partial APVD	32*	27	84	3	2	67	29	25	86

*A series of 22 patients with partial APVD was omitted when computing survival rates in the two categories (intracardiac and extracardiac drainage), because the survivals were not identified in regard to the routes of the pulmonary drainage. The over-all survival for this series of patients was 82 per cent. The series was included in "*A.*"

Table 3

Survival Rates in Total Anomalous Venous Drainage Treated Surgically

	Combined group			With EC			Without EC		
	No.	S	%	No.	S	%	No.	S	%
All cases	53	24	45	12	7	58	41	17	41
SVC	9	6	67	1	1	100	8	5	62
CS	10	6	60	5	4	80	5	2	40
PLAC	34	12	35	6	2	33	28	10	36

ventricular pressures were taken at the operating table, both before and after repair of the shunt in only four patients; in the patient with significantly elevated pulmonary vascular resistance (patient no. 4), the pressure did not fall to normal after the repair.

Radiographic and Electrocardiographic Data

Table 7 summarizes the radiologic and electrocardiographic features in these patients. Most patients showed an enlarged right atrium and right ventricle. The main pulmonary artery was consistently enlarged. Peripheral pulmonary arterial prominence varied, and did not necessarily parallel the main pulmonary artery enlargement. The two patients with markedly elevated pulmonary vascular resistance, patients nos. 4 and 5, showed normal or only slightly increased prominence of peripheral pulmonary arterioles in the face of marked main pulmonary artery enlargement, this finding being highly suggestive of increased peripheral vascular resistance. The aortic shadow was normal or hypoplastic in all patients. With the exception of the two patients with the persistent left anterior cardinal veins, it was impossible to recognize abnormal venous drainage on plain films.

All electrocardiograms showed evidence of right ventricular hypertrophy except in patient 5.

Figure 1 shows an x-ray of patient 6, who had partial anomalous venous drainage (both right and left inferior pulmonary veins draining via the coronary sinus). He had a large

Table 4

Complete Repair of Extracardiac Total Anomalous Venous Drainage

A. Total group

	Combined group			With EC			Without EC		
	No.	Complete repair	%	No.	Complete repair	%	No.	Complete repair	%
All cases	53	9	17	12	3	25	41	6	15
SVC	9	2	22	1	0	0	8	2	25
CS	10	4	40	5	2	40	5	2	40
PLAC	34	3	9	6	1	17	28	2	7

B. Surviving patients

	Combined group			With EC			Without EC		
	No.	Complete repair	%	No.	Complete repair	%	No.	Complete repair	%
All cases	24	9	37	7	3	43	17	6	35
SVC	6	2	33	1	0	0	5	2	40
CS	6	4	67	4	2	50	2	2	100
PLAC	12	3	25	2	1	50	10	2	22

Table 5

Survival Rate for Surgical Therapy Where Complete Repair of Extracardiac Total Anomalous Venous Drainage Was Attempted

	Combined group			With EC			Without EC		
	No.	S	%	No.	S	%	No.	S	%
All cases	15	9	60	7	5	71	8	4	50
SVC	3	2	67	0	—	—	3	2	67
CS	7	4	57	5	4	80	2	0	0
PLAC	5	3	60	2	1	50	3	2	67

shunt and a low pulmonary vascular resistance. The right atrium, right ventricle, and pulmonary artery are enlarged. The peripheral pulmonary vessels are markedly engorged. Figure 2 is an x-ray of patient no. 5, who also had partial anomalous venous drainage (both right pulmonary veins draining into the superior vena cava). In contrast to the previous patient, this patient had a small shunt and the highest pulmonary vascular resistance in the series. The main pulmonary artery enlargement is prominent; but peripheral pulmonary vascular shadows are virtually absent, an indication of the marked involvement of the smaller pulmonary vessels. Figure 3 represents the classical picture of total anomalous pulmonary venous drainage via a persistent left anterior cardinal vein (patient no. 8). The so-called "snow man" or "figure-of-eight" configuration can be easily recognized. Angiography offers significant advantages in the preoperative evaluation of patients with anomalous venous drainage. Figures 4 and 5 show complete pulmonary venous drainage into the coronary sinus in patient 10.

Anomalies and Surgical Repair

In general, four principles of repair were utilized in this series. In the first category are those patients whose veins drained directly into the right superior vena cava. There were six such patients; of these six, one drained one pulmonary vein into the right superior vena cava, four drained all of the right lung into the superior vena cava, and one patient drained all pulmonary veins into the superior vena cava. The highest anomalous implantation into the superior vana cava occurred 8 cm. above the cava-atrial junction. The repair in this category is illustrated in figure 6. A tunnel of Ivalon was constructed, which diverted pulmonary venous blood through the existing atrial defect into the left atrium, as first described by Kirklin.[24] This new channel

Figure 3

Posteroanterior x-ray of patient 8 (total anomalous pulmonary venous drainage via a persistent left anterior cardinal vein) demonstrates the typical "snow man" or "figure-of-eight" appearance. Upper portion of the mediastinal shadow on the right side is the distended superior vena cava and on the left side is the distended persistent left anterior cardinal vein.

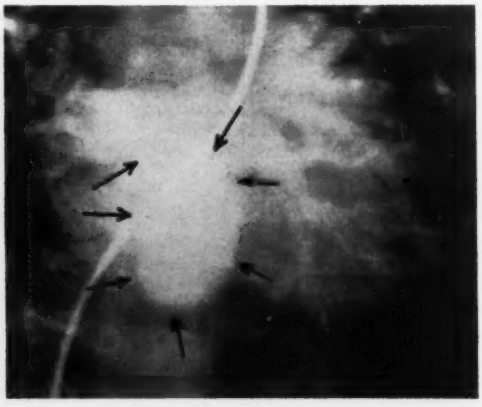

Figure 4

Radiopaque material was injected via the cardiac catheter into the pulmonary artery. The x-ray shows all pulmonary veins entering an enlarged coronary sinus (patient 10).

consisted anteriorly of the Ivalon and posteriorly of the posterior wall of the superior vena cava and the right atrium. Excessive diminution of the lumen of the superior vena cava is possible with this technic. In two instances an elliptical patch of Ivalon was implanted in the anterior aspect of the superior vena cava, in order to enlarge its diameter. In no other instance did the tunnel restrict the caval return sufficiently to cause an increase of venous pressure, which was constantly monitored by means of an inlying catheter. Since this laboratory recently has demonstrated the tendency of Ivalon to calcify and contract, Dacron and Teflon have been used exclusively for cardiac implantation.

There were two patients in whom complete pulmonary venous drainage entered a persistent left anterior cardinal vein. In the first patient, the repair consisted of (1) anastomosis of the posterior left atrium to the common pulmonary drainage system, (2) closure of the atrial septal defect, and (3) complete occlusion of the persistent left anterior cardinal vein. The entire intracardiac procedure was performed through the left atrium. This patient did not survive. The second patient was repaired with the method diagrammatically illustrated in figure 7. By entrance through the right atrium and the atrial septal defect, an incision was made in the posterior wall of the left atrium, and a portion of the right atrium. A corresponding incision was made in the pulmonary venous trunk immediately posterior to this area. An anastomosis was completed, resulting in a large fistula between the pulmonary vein and the atrial chambers. Closure of the atrial septal defect was accomplished, so that the fistula lay entirely within the newly reconstructed left atrium. This approach, advocated by Cooley and Ochsner[4] in 1957, appears to be preferable to the left atrial approach, because the right atrium is capacious and the surgical manipulations can be carried out more readily, and a larger anastomosis between the pulmonary venous drainage system and the left atrium may be constructed, reducing the possibility of obstruction to the pulmonary venous flow. The final stage of the repair is the complete occlusion of the persistent left anterior cardinal vein, which inferiorly was

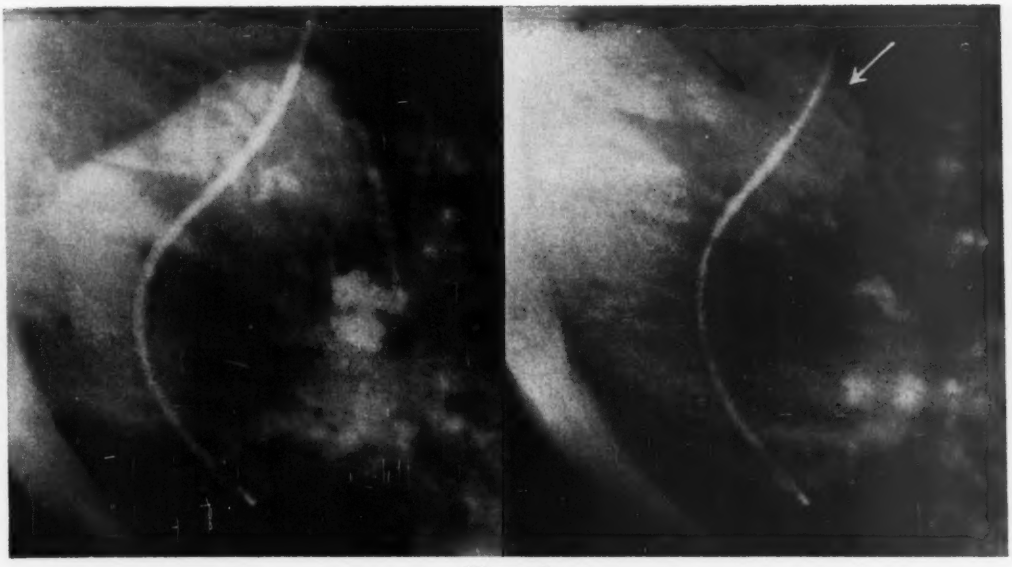

Figure 5

Left. *Lateral view of patient 10 during angiography. The posterior aspect of the coronary sinus is outlined.* Right. *Moments later, contrast material has moved from the right atrium into the right ventricular outflow tract.*

ligated flush with the pulmonary venous trunk, and superiorly was ligated flush with the innominate vein, to reduce the possibility of embolization from a venous "diverticulum." In the surviving patient, the pulmonary venous pressure was monitored during partial and complete occlusion of the persistent anterior cardinal vein. Initially, with complete occlusion, cardiac action became poor, and the venous pressure rose; but with a period of from 5 to 10 minutes of incomplete and finally complete occlusion, the pulmonary venous pressure remained stable at 10 to 12 mm. Hg. When complete repair is attempted, monitoring the pulmonary venous pressure is essential. If the pressure remains high, the

Table 6

Cardiac Catheterization Data

		Age	Sex	TPF Index	P/S	L → R Index	Vasc R. Index	ABS	Pressure RV	Pressure PA	Postoperative Fall
	Partial APVD										
SVC	1—	24	F	6.4	4:1	4.8	225	162	108/12	33/11	+
SVC	2—	12	M	10.0	2.7:1	6.2	109	80	39/6	31/12	
SVC	3—	51	M	4.7	1.8:1	2.6	204	102	56/21	45/18	+
SVC	4—	33	F	3.8	2:1	1.9	727	460	60/0		—
SVC	5—	41	M	4.3	1.7:1	1.9	829	512	89/5	63/41	
CS	6—	23	M	6.8	2.2:1	3.7	247	126		39/6	
	Total APVD										
SVC	7—	7	M	10.5	5:1	8.5	151	123	84/5	36/11	
PLAC	8—	6	F	8.2	2.8:1	6.0	216	270	30/0	30/18	
PLAC	9—	11	M	11.0	3.5:1	8.6	109	115	38/0	36/15	
CS	10—	3½	M	20+	5+:1	20+	12.5	25	51/4	22/8	+

Abbreviations: TPF index, total pulmonary flow per M.^{2} of body surface area; P/S, ratio on pulmonary to systemic flow; L→R index, left-to-right shunt flow per M.^{2} of body surface area; Vasc R., pulmonary vascular resistance expressed as dynes sec. cm.$^{-5}$; ABS, absolute.

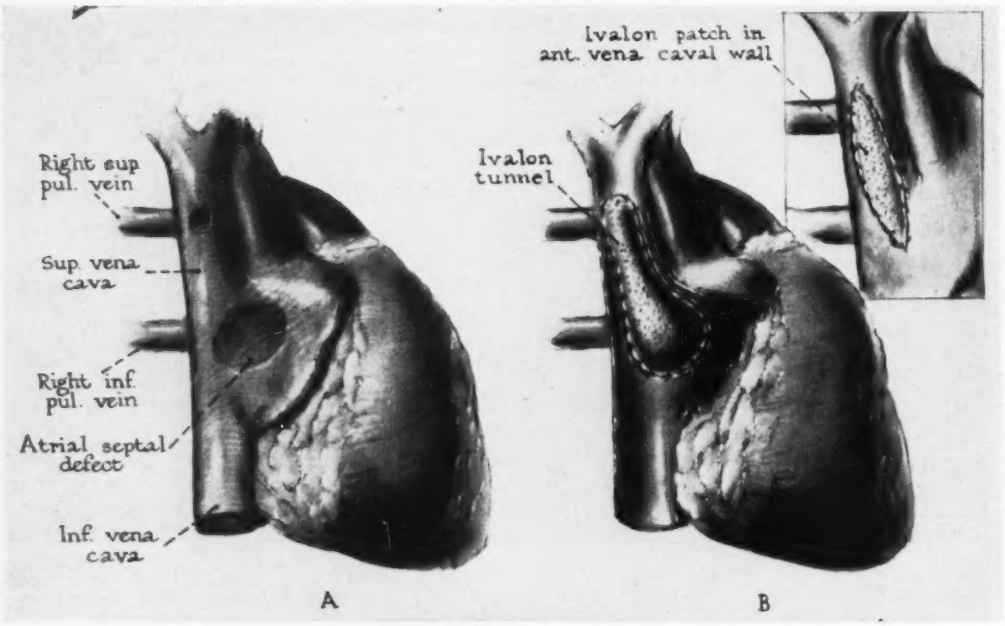

Figure 6

A. The right superior pulmonary vein is draining into the superior vena cava. The right inferior and left pulmonary veins drain into the left atrium. An atrial septal defect is present. B. Placement of a patch of Ivalon routes the flow from the right superior pulmonary vein through the compartmented superior vena cava, then through the atrial septal defect, into the left atrial chamber. An elliptical patch of Ivalon has been placed in the anterior wall of the vena cava to enlarge its cross-sectional area.

Table 7

Radiologic and Electrocardiographic Data

		Age	Sex	RA	RV	CPA	AO	PPA	AV	ECG
	Partial APVD									
SVC	1—	24	F	+	+	+	N	+	0	RVH
SVC	2—	12	M	+	+	+	N	+	0	RVH
SVC	3—	51	M	++	++	+	N	+	0	RVH
SVC	4—	33	F	CE	+	++++	−	+	0	RVH
SVC	5—	41	M	CE	N	+++	−	N	0	AF. RAD RBBB
CS	6—	23	M	+++	+++	++	−	++++	0	RVH RBBB
	Total APVD									
SVC	7—	7	M	++	++	++	−	++	0	RVH P-pulmonale
PLAC	8—	6	F	+	CE	+	−	+	PLAC	RVH
PLAC	9—	11	M	+++	+++	++	−	+	PLAC	RVH, RBBB P-pulmonale
CS	10—	3½	M	+++	+++	+++	−	++	0	RVH-RBBB P-pulmonale

Abbreviations: CPA, common pulmonary artery; AO, aorta; PPA, peripheral pulmonary arterioles; AV, anomalous veins visualized on routine films; CE, cannot evaluate; N, normal, + to ++++, degrees of enlargement.

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Table 8

Surgical Repair Data

	Age	Sex	Duration (min.) Partial EC	Total EC	Cardiotomy	Flow L./M²./min.	Anomaly			Repair
1—	24	F	45	41	39	2.0	RT upper lobe SVC	Pulmonary valvular stenosis	ASD	Ivalon tunnel + pulmonary valve commissurotomy + ASD closure
2—	12	M	31	26	23	2.3	RT lung SVC		ASD	Ivalon tunnel + ASD closure
3—	51	M	56	50	41	2.5	RT lung SVC	Tricuspid insufficiency	ASD	Ivalon tunnel + ASD closure
4—	33	F	54	47	30	2.6	RT lung SVC		ASD	Ivalon tunnel & Ivalon patch on SVC + ASD closure
5—	41	M	49	42	39	2.5	RT lung SVC		ASD	Ivalon tunnel + Ivalon patch on SVC + ASD closure
6—	23	M	40	38	35	2.7	RT & left inf. lobes coronary sinus	Tricuspid insufficiency	ASD	Dacron closure coronary sinus + tricuspid annuloplasty + ASD closure
7—	7	M	39	37	33	1.6	RT & left lungs SVC		ASD	Ivalon closure + 90% ASD closure
8—	6	F	28	26*	14	1.2	RT & left lungs PLAC		ASD	Persistent ant. cardinal vein and anastomosed to left atrium + interruption of ant. card. vein + ASD closure
9—	11	M	64	59	55	2.1	RT & left lungs PLAC		ASD	Persistent ant. cardinal vein anastomosed to post. L.atrium (& R.atrium) + atrioseptopexy with closure of ASD + interruption of ant. card. vein
10—	3½	M	38	34	31	2.6	RT & left lungs CS		ASD	Incision common wall of L.atrium & coronary sinus + atrioseptopexy with ASD closure
	Mean		44	40	34	2.2				

*Potassium arrest used.

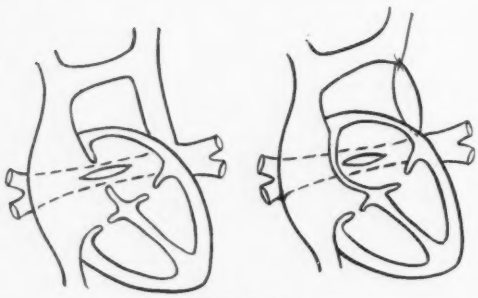

Figure 7

The first stage of repair of total anomalous pulmonary venous drainage into a persistent left anterior cardinal vein is shown diagrammatically on the left. An incision into the posterior left (and right) atrial wall and into the right pulmonary venous trunk immediately posterior is shown. After the anastomosis is completed, the atrial septum is sutured to the right of the created fistula, and the persistent left anterior cardinal vein is ligated flush with the innominate vein and the left pulmonary venous trunk.

left anterior superior cardinal vein should not be completely interrupted, but rather, only partially and consistent with adequate cardiac function. Presumably, adaptation will occur, and at a subsequent thoracotomy this safety valve may be further diminished or completely interrupted. It has been our experience that impedance of pulmonary outflow of even minor degree and for brief periods is extremely hazardous, particularly in the small patient.

Two patients had anomalous venous drainage via the coronary sinus. One patient drained both inferior pulmonary veins into the coronary sinus (an anomaly that has not been previously reported in the surgical literature), and the second patient drained all of the pulmonary veins into the coronary sinus. Figure 8 illustrates diagrammatically the anomaly and its repair. The common wall of the coronary sinus and the left atrium was incised or excised and the atrial septum was reconstructed to encompass all of the new ostium into the left atrium. This method has the theoretical disadvantage of allowing the desaturated coronary sinus blood to drain directly into the systemic side of the heart. In the surviving patient with this repair, however, measurable oxygen desaturation has not occurred.

In table 8 are listed some of the data related to surgical repair. Perfusion times varied between 28 and 64 minutes, with a mean of 44 minutes. Flows average 2.2 L./M.^{2} per minute. Patients 7 and 8 were done early in the series, when lower flows were utilized. The repair listed for patient 6, "Dacron closure," is actually a surgical error, which deserves further comment.

Mortality

There were three deaths in this series of 10 patients, none of which could be directly attributed to the perfusion. A brief review of the deaths follows:

Case Reports

Case 1

Patient 8 was a 6-year-old girl, who had total anomalous pulmonary venous drainage via a persistent left anterior cardinal vein. The common venous channel was anastomosed to the left atrium. The atrial septal defect was closed and tentative occlusion of the persistent left anterior cardinal vein caused cardiac slowing. During an interval of time, the persistent anomalous vein was intermittently, and then finally, occluded, as it appeared tolerated. Postoperatively, the patient deteriorated rapidly and died. In retrospect, the anastomosis between the pulmonary venous system and the left atrium may have been inadequate. Obviously, if any question exists regarding this important point, it is mandatory to leave an avenue for decompression, either through partial repair of the atrial septal defect, or partial constriction of the anterior cardinal vein. (As the result of this experience, in the next patient operated upon with total anomalous venous drainage, patient 7, a small defect was left in the "Ivalon" atrial septum for decompression. The patient still has this partial shunt, but it is not clinically significant, and it is anticipated that a subsequent closure can be easily accomplished without the need for cardiotomy.) As indicated earlier, the second patient with a persistent left anterior cardinal vein was successfully repaired with the technic described and illustrated above, with a total correction (figure 7).

Case 2

Patient 6 was a 23-year-old man, with a large left-to-right shunt, thought to be due to an atrial septal defect. At the age of 16, an attempt at

repair was made elsewhere, under hypothermia. Cardiac arrest occurred, and a thoracotomy with massage was carried out successfully but the procedure was discontinued. At exploration 7 years later, the pericardium was densely adherent to the epicardium, necessitating a tedious dissection to expose the right lateral aspect of the heart. Further dissection was thought not necessary as the diagnosis appeared straightforward and the density of the adhesions raised the problem of possible injury to the coronary vessels. Routine exploratory elevation of the heart out of the pericardial sac to visualize the pulmonary venous inflow on the posterior aspect of the left atrium, therefore, was not performed. Had this been done, the correct anatomic diagnosis would have been suggested and error avoided. As the right atrium was opened, two 3-cm. defects were seen; and as the finger was passed through the upper defect, the mitral valve could be felt. Bright red blood drained through both defects, and the situation was erroneously interpreted as a fenestrated atrial septal defect. The upper defect was closed by direct suture, and the lower was closed with a Dacron patch. The coronary sinus orifice was never identified. The patient died 48 hours postoperatively, showing evidence of progressive pulmonary edema and output failure. At autopsy, the lower defect, which was closed, was an enlarged coronary sinus ostium, into which both right and left inferior pulmonary veins drained. Closure resulted in venous infarction of the heart and both lower lobes of the lung.

Case 3

Patient 5 was a 41-year-old man, diagnosed as having an atrial septal defect, with fixed pulmonary arteriolar changes. The patient had the highest pulmonary vascular resistance in this series, and during preoperative discussion, the patient was rejected for surgery because of the poor operative prognosis. Because of preliminary reports of possible improvement in patients with pulmonary arteriolar changes with long-term heparin therapy, this patient was maintained in a heparinized state for 3 months, and then recatheterized. No improvement was noted in the pulmonary vascular resistance. The patient's symptoms became worse, and though the risk was considered to be high, surgery was performed. The right pulmonary veins drained into the superior vena cava; they were funneled into the left atrium through the atrial septal defect with an Ivalon tunnel. Immediately postoperatively, the patient did well, and showed no abnormality except for some tachypnea. By the second postoperative day, tachypnea increased and apprehension became manifest, and sudden death followed. This is not an uncommon sequence in patients with fixed pulmonary vascular resistance. At autopsy, transection of the lung revealed markedly sclerotic small vessels.

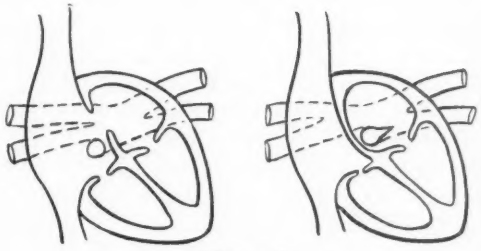

Figure 8

On the left, drainage of the pulmonary veins into the coronary sinus is diagrammatically indicated. An atrial septal defect is present. Repair is illustrated on the right, and consists of an incision and excision of the common wall of the anterior coronary sinus and posterior left atrium (and a portion of the right atrial wall) and a shift of the atrial septum to the right so that the newly enlarged coronary sinus ostium empties into the left atrium.

Summary

The English surgical literature was reviewed for a 10-year period between 1950 and 1960. A total of 166 patients with anomalous pulmonary venous drainage treated surgically was found. Of this number, 65 patients had total anomalous pulmonary venous drainage (40 per cent). Ninety-five patients (57 per cent) had anomalous venous drainage via *extracardiac channels*. The over-all survival rate for 166 patients was 74 per cent. The single lesion with the lowest survival rate (35 per cent) was total anomalous pulmonary venous drainage via a persistent left anterior cardinal vein. Of the 34 patients in this category, only three (9 per cent) had a complete repair of the anomalous drainage with survival.

A series of 10 patients with anomalous venous drainage via *extracardiac channels* operated on with the aid of extracorporeal circulation is reported. There were three deaths. Drainage occurred via the superior vena cava (six patients), the coronary sinus (two patients), and a persistent left anterior cardinal vein (two patients). Included in

the series is a fourth instance of successful complete repair of total anomalous pulmonary venous drainage via a persistent left anterior cardinal vein. The clinical features, methods of repair, and perfusion data are reviewed.

An important aspect of treatment for total anomalous pulmonary venous drainage is the realization that impedance of pulmonary venous outflow is extremely hazardous. It is suggested that pulmonary venous pressure be monitored when complete repair is contemplated. If complete occlusion of decompressive channels causes a significant increase in the pulmonary venous pressure, some avenue of decompression should be left; otherwise, venous infarction of the lungs with probable fatality will result.

Acknowledgment

The authors wish to thank particularly Dr. Melvin M. Figley of the Department of Radiology, and also Drs. Robert A. Bruce, Leonard A. Cobb, and Kenneth M. Eyer of the Division of Cardiology, and Dr. Warren G. Guntheroth of the Department of Pediatric Cardiology for their valuable assistance in the evaluation of the diagnostic data in this series of patients presented.

Addendum

Since submission of this article, two additional patients with extracardiac anomalous pulmonary venous drainage have been successfully corrected with the aid of extracorporeal circulation. One patient, aged 42 years, with total right anomalous pulmonary venous drainage and atrial septal defect was similar to case 5, table 8. The correction was identical except for the use of a Teflon-knitted prosthesis rather than Ivalon. The second patient, aged 17 years, was diagnosed preoperatively as total anomalous pulmonary venous drainage into the lower portion of the superior vena cava and atrial septal defect. At surgery, all pulmonary veins, with the exception of the left inferior pulmonary vein, emptied into the superior vena cava and right atrium. The left inferior pulmonary vein emptied into the left atrium in relatively normal position. Again, a Teflon-knitted prosthesis was used for total correction. Both patients have done well.

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An account of formative influences which have affected a career should quite properly start with inheritance. It may not be possible to trace the appearance of many traits from generation to generation through a considerable past—the combinations of determinative factors become too complicated as the numbers in the ancestry multiply. Sometimes, however, the transmission of the infinitesimal hereditary packets in germ cells is demonstrated by peculiar features clearly distinguishable in a long family line. The famous Hapsburg lip is an eminent example. . . . . Besides biological inheritance there is tradition to be recognized as a potent agency in affecting behavior.—WALTER B. CANNON, M.D. New York, W. W. Norton & Co., Inc., 1945, p. 11.

Atrial Flutter with Irregular Ventricular Response as a Contraindication to Digitalis

By SEYMOUR B. LONDON, M.D., AND ROSE E. LONDON, M.D.

ALTHOUGH atrial flutter occurs at atrial rates of 250 to 350 per minute, or faster, the ventricular response is usually at one half the atrial rate because of partial block of atrioventricular conduction. This block is of physiologic origin, arising from the refractory period of the atrioventricular node, and it may occur without obvious cardiac disease.[1-3] On the other hand, variations in the ventricular response during atrial flutter[4] indicate increased block, which may be associated with disorders of the conduction system.

Two cases are presented that illustrate the potential danger of producing complete atrioventricular block by the use of digitalis in atrial flutter with greater than 2:1 block and emphasize the value of an external electric cardiac pacemaker in ventricular asystole that may follow such complete block.

Case Reports

Case 1

A 58-year-old woman with no history of cardiovascular disease or hypertension was found on a routine examination to be in good health except for a grossly irregular rapid heart action. The pulse rate varied between 120 and 130, and the blood pressure was 120/80. The heart tones were of good quality, there were no murmurs, and there were no signs of enlargement or failure. An electrocardiogram (fig. 1) demonstrated atrial flutter with 2:1 and 3:1 ventricular response with Wenckebach phenomenon. The atrial flutter rate was approximately 300 and the ventricular rate 130.

Although the patient felt well, it was thought wise to correct the arrhythmia. She was hospitalized and was given 1 mg. of digoxin in divided doses. On the following day, an additional 0.5 mg. of digoxin was given. The atrial flutter persisted but now with fixed 4:1 block (fig. 2A). Because of the continued flutter three doses of 0.2 Gm. of quinidine were given three hours apart. By the evening of the second day variable block had recurred with resultant irregularity of the pulse; an additional 0.25 mg. of digoxin was given. The next morning the electrocardiogram revealed a flutter wave rate of 300 and an irregular ventricular rate of approximately 60 (fig. 2B). Digoxin was discontinued because of the increased atrioventricular block, but quinidine was continued and the patient received five 0.2-Gm. doses at 3-hour intervals. At 8:00 A.M. on the fourth day, with an electrocardiogram (fig. 2C) showing no change from the previous day, the patient was given 0.25 mg. of digoxin, making a total dose of 2 mg. over 4 days. One hour later the patient suddenly vomited and fell out of bed. She recovered quickly but had four similar episodes during the next 4 hours. Each seizure, as described by the nurses, consisted of nausea, flushing of the skin, and transient unconsciouness, followed by pallor and perspiration. During the third seizure, an electrocardiogram (fig. 3) revealed persistent atrial flutter and long periods of ventricular asystole. Immediately an external electric pacemaker* was applied and further seizures were terminated promptly by electric stimulation.

A trial of isoproterenol (Isuprel) sublingually, 7.5 mg. at 10-minute intervals was followed by temporary 2:1 atrioventricular response and frequent ventricular extrasystoles. Ten minutes after the third dose of isoproterenol, however, ventricular standstill of 12 seconds occurred and was associated with a major convulsive seizure. Therefore the heart was driven intermittently by the pacemaker for the next 12 hours until 4:1 to 6:1 atrioventricular conduction returned with a ventricular rate of 60 to 70. Thereafter the patient regained her usual state of well-being, and was discharged without further medication. Electrocardiograms showed persistent atrial flutter with variable block until approximately 1 year later, when she was found to have a normal sinus mechanism with entirely normal tracing. (fig. 4). She has remained well since.

Case 2

A 74-year-old retired iron worker had suffered a myocardial infarction 6 years previously followed by congestive failure, which was controlled by digitalis and salt restriction. His electrocardiograms (fig. 5) over the previous 2 years showed complete right bundle-branch block and a pro-

From the Miami Heart Institute, Miami Beach, Florida.

*Pacemaker-Monitor, PM-65, Electrodyne Co., Norwood, Massachusetts.

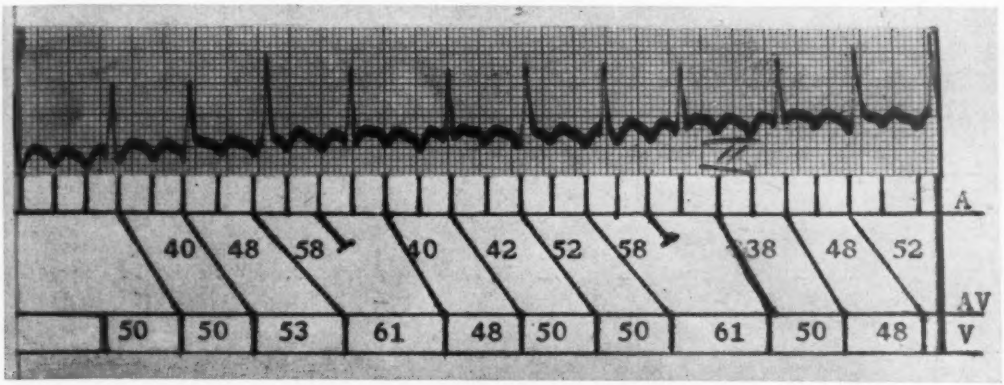

Figure 1

Case 1. Lead II demonstrating atrial flutter with variable F-R relationship and Wenckebach phenomenon. AV represents the time between the atrial flutter impulse (A) and the ventricular activation (V). Alternate flutter impulses showing physiologic block are not indicated as penetrating the AV node. The interrupted oblique lines following flutter wave numbers 10 and 20 indicate a block of the impulse in the AV node producing Wenckebach phenomenon.

longed P-R interval of 0.30 second. Over the period of 3 years, he developed repeated syncopal episodes. He was hospitalized because of syncopal attacks and varying cardiac rhythms (fig. 6A and B). Because of increasing congestive heart failure he was given 2.25 mg. of digoxin over a 4-day period.

Despite several Stokes-Adams seizures of short duration, he improved by the fifth hospital day, being alert, talkative, and without complaints. On the morning of the final hospital day the patient became extremely cyanotic and unresponsive, and sweated profusely. An electrocardiogram at this time showed atrial flutter with complete heart block. Over a period of an hour the patient's condition deteriorated and complete ventricular asystole occurred with persistent atrial flutter (fig. 7). Accordingly, the external electric pacemaker was applied, and the blood pressure and pulse rate were maintained artificially for 10 hours. No spontaneous ventricular activity appeared during this time, and gradually the clinical status deteriorated, despite the use of metaraminol and levarterenol in large quantities. The urinary output was good but the respiratory rate gradually slowed and eventually stopped, and the ventricles failed to respond to further excitation of the pacemaker.

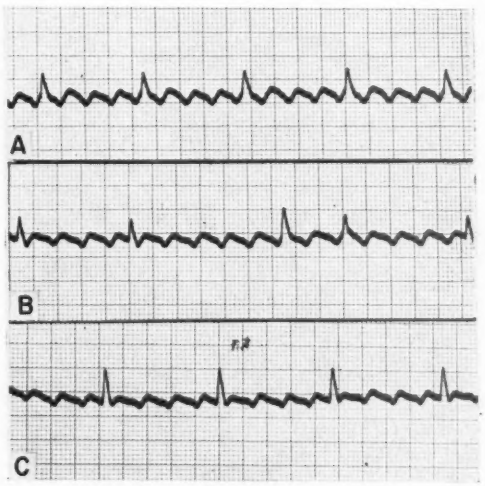

Figure 2

A. *Case 1. Fixed 4:1 block following digitalization Second hospital day. (Lead aV_F.)* B. *Case 1. Increase in block on third hospital day with further digitalization. (Lead aV_F.)* C. *Case 1. Tracing taken 1 hour prior to onset of Stokes-Adams seizure on fourth hospital day. (Lead aV_F.)*

Discussion

The determining factor in each case appeared to be not the dosage of digitalis used but rather the pre-existing abnormality of conduction of the atrioventricular node. The addition of small doses of digitalis to an already impaired atrioventricular node, resulted in the production of partial to complete heart block with absence of nodal or ventricu-

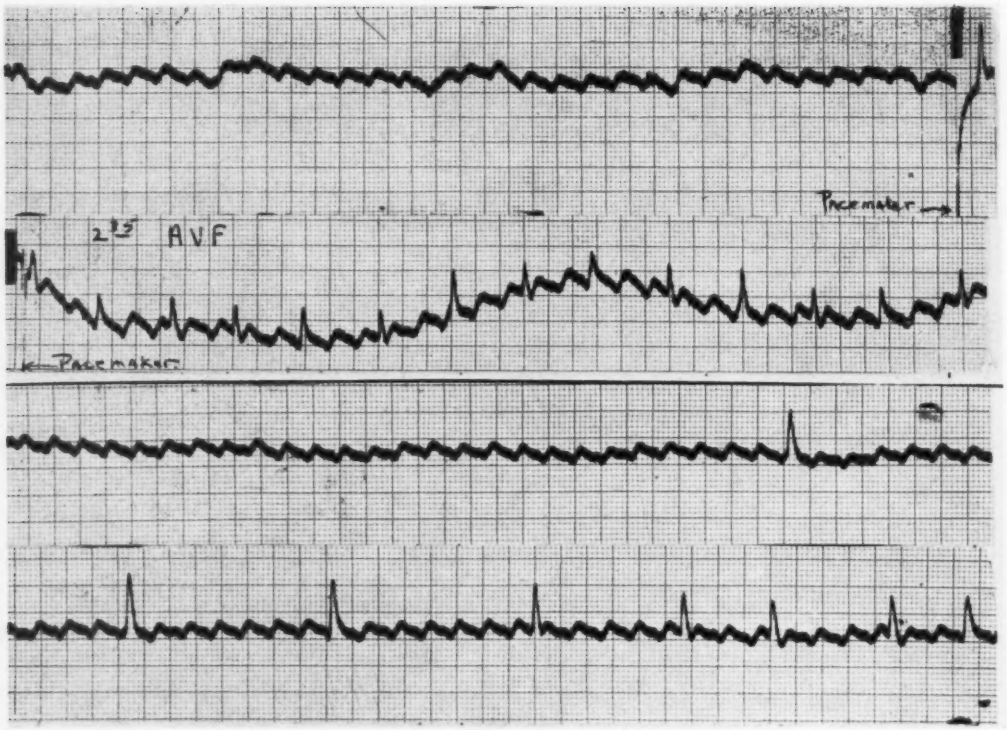

Figure 3

Case 1. Sections of continuous electrocardiogram demonstrating prolonged ventricular asystole interrupted by pacemaker (indicated by solid block) and short periods of irregular ventricular activity followed by prolonged ventricular asystole. Fourth hospital day. (Lead aV_F.)

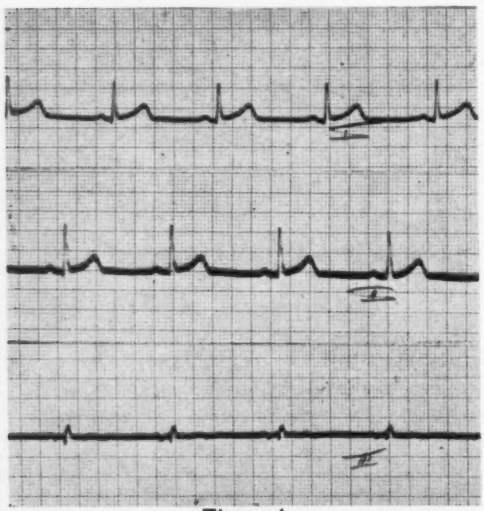

Figure 4

Case 1. One year later. Leads I, II, and III showing spontaneous conversion to normal sinus rhythm.

lar escape. In the second case, prior to the onset of atrial flutter, there was first-degree heart block with a P-R interval of 0.30 second. In the first case, the depression of the atrioventricular node was manifest by the irregular ventricular response, which occurred in a pattern indicative of first- and second-degree atrioventricular block of the Wenckebach type (fig. 1). This important consideration is well pointed out by Besoain-Santander, Pick, and Langendorf,[4] who considered the presence of an atrioventricular ratio greater than 2:1 to be evidence of a "disturbance of atrioventricular conduction corresponding to P-R prolongation during sinus rhythm." The clinical importance of this electrocardiographic sign is attested by our two cases in which proper appreciation of atrioventricular depression might have prevented the serious consequences of drug therapy.

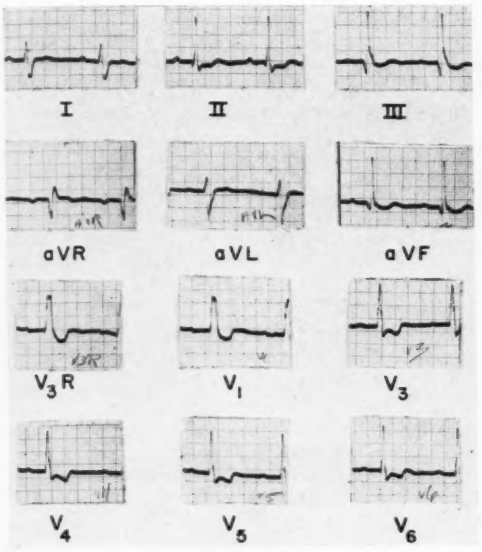

Figure 5

Case 2. Electrocardiogram demonstrating prolonged AV conduction with normal sinus rhythm.

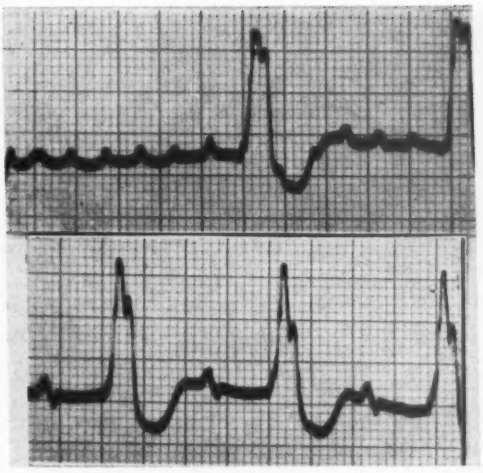

Figure 6

Top. *Case 2. V_1 on the day of admission demonstrating atrial flutter with irregular ventricular response.* Bottom. *V_1 on following day showing normal sinus rhythm.*

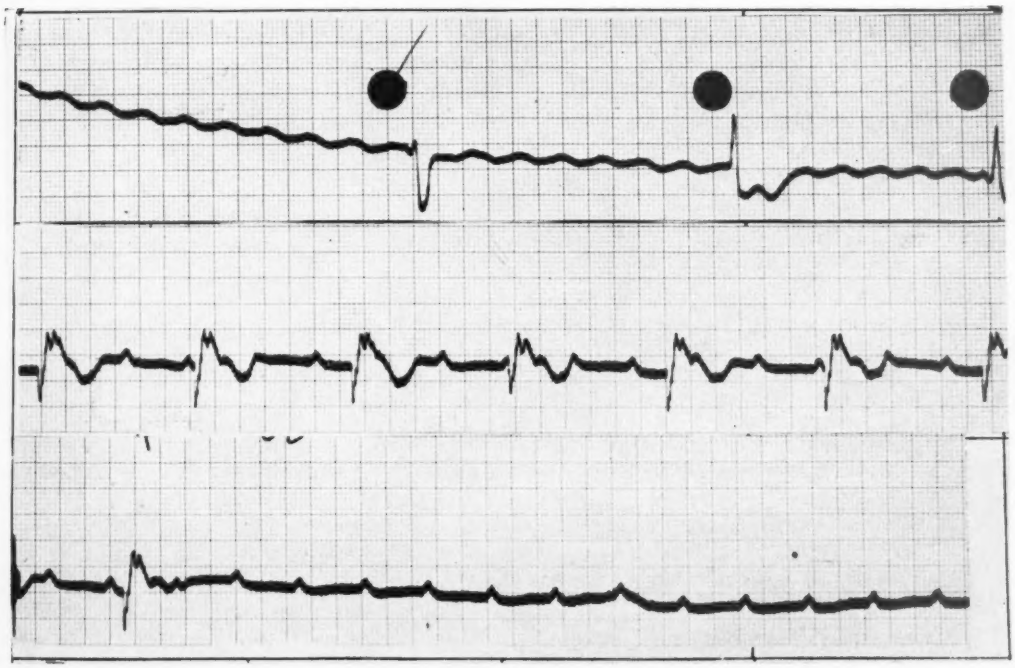

Figure 7

Case 2. Upper tracing shows atrial flutter with complete heart block and ventricular asystole with ventricular response to percussion (indicated by black dots). Middle tracing shows pacemaker driving the ventricle and atrial tachycardia. Lower tracing shows absence of spontaneous ventricular activity on discontinuation of pacemaker.

In view of the possibility of producing atrioventricular block during the conversion of atrial flutter to sinus rhythm, it is well advised that constant cardiac monitoring, with a pacemaker-monitor be undertaken in all cases showing impaired conduction. Certainly in the first case, the use of an electric pacemaker[5, 6] was lifesaving in maintaining ventricular activity until the drug effects had subsided.

Summary

Digitalis may have an additive effect on impaired atrioventricular conduction, so that atrial flutter with variable ventricular response may progress to complete heart block with ventricular asystole.

Two cases are presented of atrial flutter with variable ventricular response in whom ventricular standstill occurred during digitalis therapy.

External electric stimulation of the heart can maintain the circulation in digitalis-induced ventricular standstill.

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Do not rashly use every new product of which the peripatetic siren sings. Consider what surprising reactions may occur in the laboratory from the careless mixing of unknown substances. Be as considerate of your patient and yourself as you are of the test-tube.—SIR WILLIAM OSLER. *Aphorisms from His Bedside Teachings and Writings.* Edited by William Bennett Bean, M.D. New York, Henry Schuman, Inc., 1950, p. 103.

Control of Ventricular Tachycardia by Direct Cardiac Electric Shock

By J. K. Clarebrough, F.R.A.C.S., F.R.C.S., and I. Hopkins, M.B.

VENTRICULAR TACHYCARDIA is a not uncommon abnormality of cardiac rhythm and is usually associated with some form of organic heart disease. It may follow myocardial infarction or be associated with heart failure occurring as a result of systemic hypertension. In a small percentage of cases no obvious cause can be found.

Conversion of the abnormal rhythm by simple measures such as breathholding, carotid pressure, and pharyngeal stimulation, is much less likely than in atrial tachycardia. The usual treatment is by drug therapy of which quinidine and procaine amide are the most commonly employed.

This case report concerns a patient who developed ventricular tachycardia following a probable myocardial infarct. The abnormal rhythm could not be converted by any of the customary medical measures. When peripheral circulatory failure had occurred and death was imminent, surgically induced cardiac arrest converted the rhythm to normal with full recovery.

Case Report

M. H., a 67-year-old invalid pensioner, gave a history that he had sustained a shrapnel wound to the chest in 1918 but no serious consequences developed. In the same year he had an operation for urethral stricture. In 1955, following an abdominal injury, he developed a perineal cellulitis, and a permanent suprapubic cystostomy was established. Two attacks of cardiac syncope are recorded as having occurred during the hospital admission. His blood pressure was noted as 180/80.

On December 16, 1958, the patient was admitted with a 12-hour history of substernal pain radiating to the left shoulder. The pulse was 140, with extrasystoles, and the blood pressure was 135/85. The electrocardiogram showed evidence of myocardial ischemia (fig. 1). Despite an episode of mild cardiac failure, the patient made an uneventful recovery and was discharged on quinidine and chlorothiazide.

In July 1959, the patient was re-admitted with nausea and vomiting for 12 hours. There had been no chest pain. The pulse rate was 204 per minute, the blood pressure was 105/70, and the jugular venous pulse was elevated to 3 cm. above the sternal angle when the patient was semirecumbent at 45°. The electrocardiogram showed ventricular tachycardia (fig. 2). The serum glutamic oxaloacetic transaminase (SGOT) following admission was 250 units.

Carotid pressure, breathholding, and pharyngeal stimulation failed to convert the arrhythmia. Procaine amide, 1 Gm., was given intravenously in 5 minutes without effect and was followed immediately by rapid digitalization because of the heart failure. On the day following admission quinidine sulfate was commenced. The dosage of the drug was increased over the ensuing 7 days until the eighth day when 6 Gm. were given over 12 hours in divided doses. This was combined with atropine sulfate, 1.2 mg., for three doses. Some slowing of the pulse was achieved with spreading of the QRS complexes but no conversion of the rhythm (fig. 3).

Digitalis was then stopped and 1.5 Gm. of procaine amide was given intravenously in 5 minutes followed by 0.25 Gm. orally every 4 hours. The arrhythmia persisted, and by the next day the patient's general condition had deteriorated considerably. There was marked peripheral cyanosis, and the jugular venous pressure was raised 5 cm. above the sternal angle. The blood pressure varied between 80 and 100 mm. Hg systolic. The patient was cold, sweating, and in peripheral circulatory failure. Considerable sacral edema was present, and the urinary output had decreased considerably over the last 24 hours.

It was considered at this stage that unless the rhythm could be converted the patient would be dead within a few hours. It was decided to attempt external conversion by electric shock. The patient was taken to the operating theater and given light anesthetic with pentobarbital and fluothane. Electrodes were applied in varying positions over the left chest, and electric shocks at 180 volts for 1 second were applied without effect. A higher

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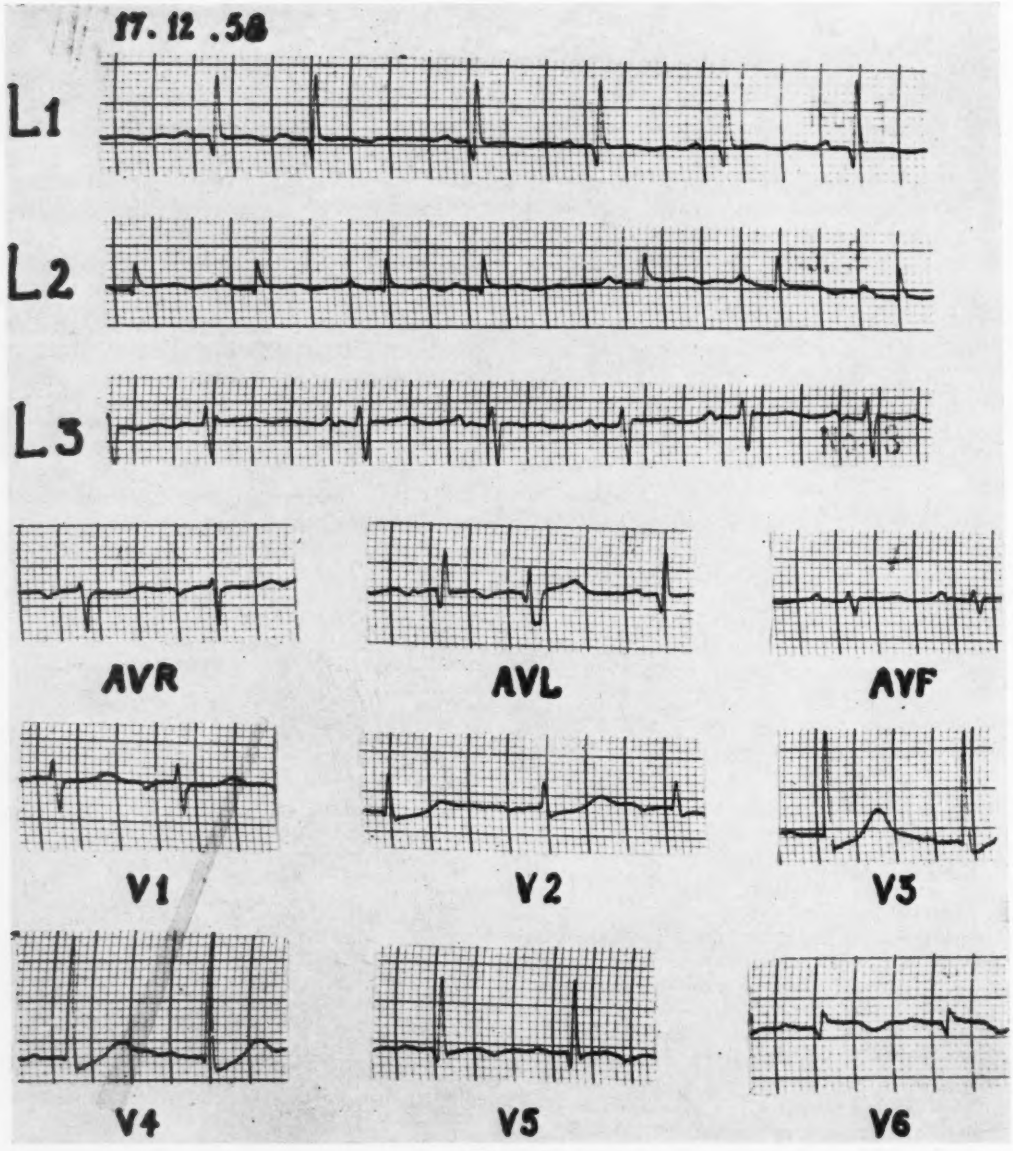

Figure 1

Electrocardiogram done in December 1958, showing evidence of myocardial ischemia.

voltage was not obtainable with the equipment available at that time. At this stage the blood pressure was unrecordable. A small left anterolateral thoracotomy was performed and the pericardium was opened. The heart was considerably dilated and beating weakly at a rate of 140 to 160 beats per minute. The electrodes of the standard, internal defibrillator were then applied across the base of the left ventricle. Two shocks of 110 volts each for 0.1 second were applied. The heart immediately stopped. Massage was commenced and cardiac contraction quickly recommenced, with rapid improvement in ventricular tone. The rhythm varied from normal to some

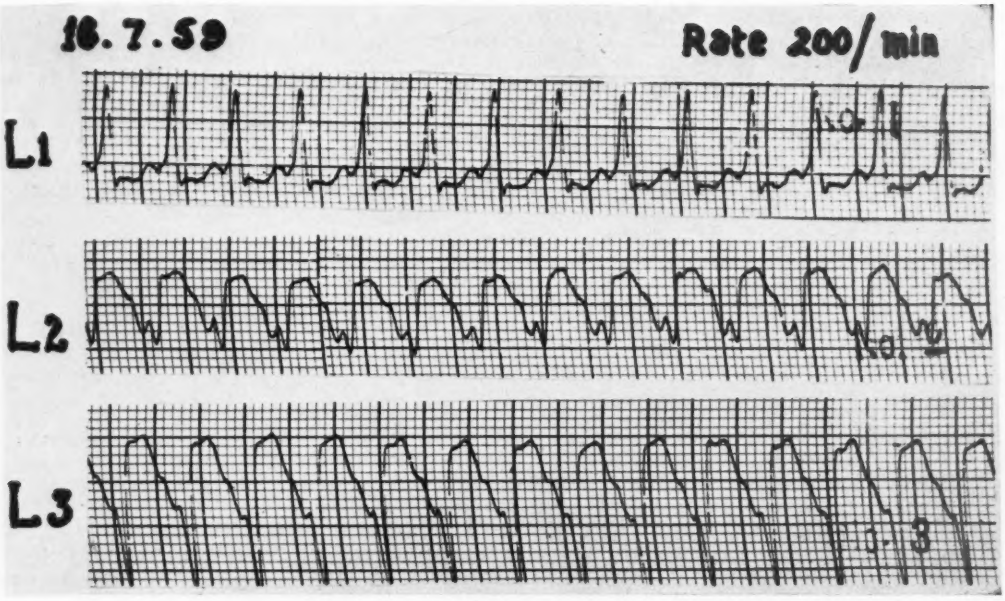

Figure 2

Electrocardiogram on admission showing ventricular tachycardia with a rate of 200 beats per minute.

degree of heart block (fig. 4). As cardiac rhythm and tone remained satisfactory, the chest was closed with drainage.

Despite a period of marked oliguria in the immediate postoperative period, the patient made a satisfactory recovery and was discharged from the hospital well, on the tenth postoperative day. Varying degrees of heart block persisted for the first week but normal rhythm with a few extrasystoles became established and has persisted ever since. The patient is now well 6 months after operation. He is maintained on 0.2 Gm. of quinidine daily and 500 mg. of chlorothiazide twice daily.

Discussion

In view of the previous history of myocardial ischemia and the high SGOT on admission it is reasonable to assume that an episode of infarction had precipitated the onset of tachycardia in this man. In attempting to convert the rhythm by medical means quinidine was given to the limit of tolerance as wide spreading of the QRS complexes occurred on the dosage reached. When oral quinidine fails, intravenous quinidine has been used[1] but it was thought in this case that success with this would be unlikely. The dosage of procaine amide was high but recent experience suggests that it should be carried to a higher dosage than was used here.

External control of ventricular standstill and paroxysmal tachycardia by electric shock has been reported in many cases. Zoll[2] reported 532 episodes of abnormal rhythms and included in these are eight cases of paroxysmal tachycardia controlled by external countershock. He found that voltages up to 400 volts were required in some cases.

In this patient external control by electrical countershock seemed the next step after failure of medical measures. It illustrates the fact that apparatus delivering only up to 200 volts is insufficient for external countershock. It further shows that when such equipment is not available, the standard internal defibrillator delivering 100 volts applied directly to the heart may control ventricular tachycardia with successful recovery.

Now that more adequate types of apparatus for electric countershock have become avail-

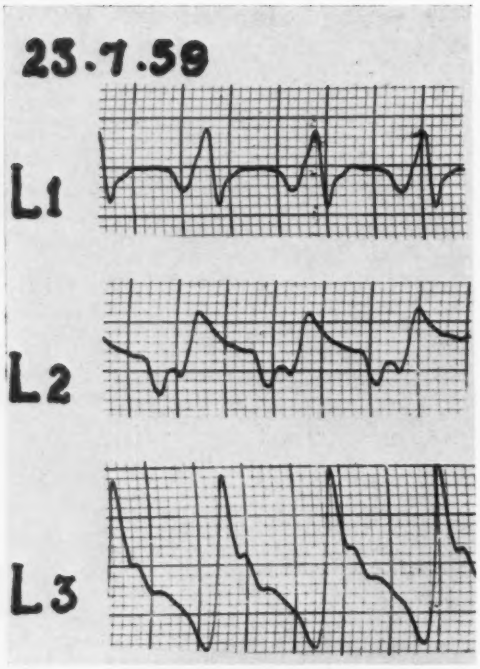

Figure 3

Electrocardiogram taken following maximum dosage of quinidine of 6 Gm. over 12 hours. Some slowing (rate 130 per minute), with spreading of the QRS complexes, has occurred.

able, external control of paroxysmal ventricular tachycardia should be attempted as soon as it is clear that medical management is not securing control of the abnormal rhythm and failure of the circulation is ensuing. In the event that the standard internal defibrillator is the only apparatus available, or external shock fails, direct application of the electrodes to the heart may be necessary to terminate the abnormal rhythm.

Summary

A case is presented of ventricular tachycardia occurring following myocardial infarction. When medical measures failed to convert the rhythm to normal, direct cardiac electric shock was employed, with return to normal of the cardiac rhythm and recovery of the patient.

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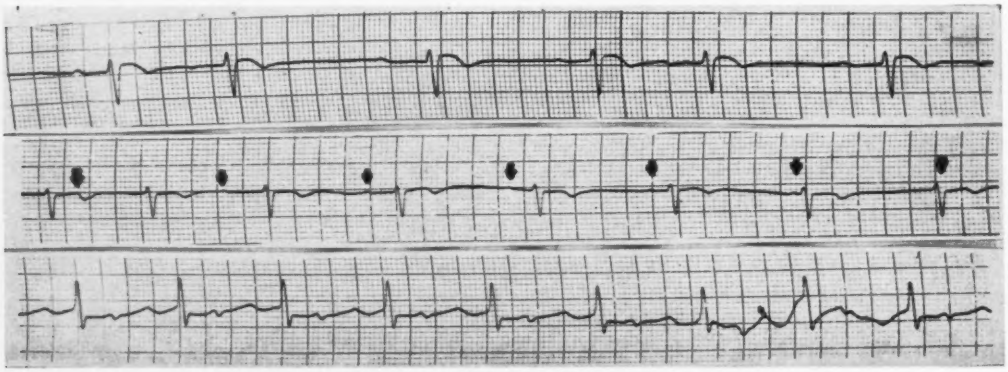

Figure 4

Electrocardiograms taken on successive days following control of abnormal rhythm show varying degrees of heart block. Top. *July 28, 1959, wandering pacemaker.* Middle. *July 29, 1959, complete heart block.* Bottom. *July 30, 1959, First degree heart block.*

CLINICAL PROGRESS

Intracardiac Myxomas with Report of Two Unusual Cases and Successful Removal

By JOHN T. DIFFERDING, M.D., RICHARD E. GARDNER, M.D., AND BENSON B. ROE, M.D.

UNTIL 1951 no intracardiac myxomas had been diagnosed before death. Since then at least 43 cases have been diagnosed during life; 27 of these were discovered during closed operations for suspected mitral or tricuspid stenosis.[1] From March 1955, when Crafoord[2] first reported the successful removal of an intracardiac myxoma, to December 1960 at least 43 successful surgical removals have been reported. This report adds two additional cases, both with unusual features.

In the first case the patient underwent successful removal of a myxoma by a closed method following accidental dislodgment of the tumor during exploration of the mitral valve. This is the second reported complete removal of such a tumor without the aid of extracorporeal circulation or inflow occlusion.

The second case is that of a 12-year-old boy who had a femoral artery embolus that on microscopic examination proved to be myxoma. The intracardiac tumor was successfully removed. This is the second patient successfully operated upon in whom a tissue diagnosis was established preoperatively. He is also the second youngest patient to survive removal of the tumor.

Case Reports

Case 1

A 55-year-old white woman had a 1-year history of repeated respiratory infections and progressive dyspnea. She had been treated for one episode of acute pulmonary edema and had responded to digitalization and diuretics.

Physical examination revealed slight cardiomegaly, normal sinus rhythm at 84, and blood pressure of 130/80. The mitral first sound was slightly accentuated, but the pulmonic second sound was normal. A grade-I diastolic murmur was heard when the patient was on her right side. No opening snap was heard. The lungs were clear.

Right-sided heart catheterization revealed a pulmonary artery wedge pressure of 29 mm. Hg and a pulmonary artery pressure of 64/30. The calculated mitral valve area was 1.2 cm.[2]

A left posterolateral thoracotomy was performed on February 18, 1960, after a preoperative diagnosis of mitral stenosis had been made. When a finger was introduced through the left atrial appendage a firm, smooth, egg-sized tumor was encountered. The mitral valve was normal in structure and function except for partial occlusion by the mass. It was planned to withdraw and approach this lesion under direct vision with extracorporeal circulation. When the tumor was palpated to determine the size and location of its attachment, however, it was inadvertently dislodged; immediate removal became mandatory because of the ball-valve action that totally obstructed the circulation when the operator's finger did not protect the valve.

The left-sided operative approach and the need to maintain a finger in the atrium made it impossible to prepare for inflow occlusion. Despite the hazard created by the tumor's size and the inevitability of a significant atrial tear, the mass was forcibly extruded through the atriotomy. Massive bleeding occurred followed by ventricular fibrillation. The rent was rapidly sutured closed, the blood was replaced, and the circulation was restored by manual systole. Defibrillation was successful after 30 minutes. The patient had an uneventful recovery without evidence of neurologic or renal damage, and her symptoms have been relieved.

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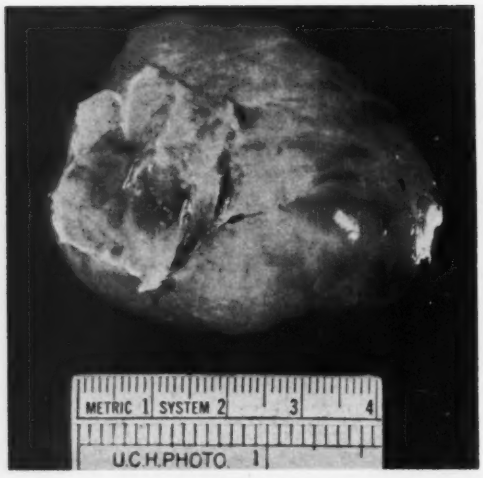

Figure 1

Myxoma of the left atrium showing the smooth glistening external surface and the rough, pedunculated base of the tumor.

Pathologic examination of the tumor showed a white and light yellow mass, 5 by 4 by 3 cm., which weighed 38 Gm. (fig. 1). A 2 by 2 cm. roughened area was present at one end where the tumor was attached to the atrial wall. The rest of the surface was smooth and glistening.

On microscopic study the central part of the tumor was composed of finely vacuolated eosinophilic material that contained numerous vascular channels and tiny islands of spindle-shaped and multinucleated cells. No mitoses were seen. The walls of the vascular channels consisted of spindle cells, frequently several cells thick, which were continuous with endothelial cells lining the lumen. The spindle cells were separated by vacuolated pale basophilic material (figs. 2 and 3). The stroma contained a moderate number of lymphocytes and plasma cells, lesser amounts of neutrophils and macrophages, numerous foci of calcification, some recent hemorrhage, and small clumps of golden brown pigment. A thin rim of dense eosinophilic material on the surface of the tumor contained a few flattened endothelial cells and overlay a thicker layer of vacuolated light basophilic material.

Case 2

A 12-year-old boy was hospitalized in November 1959 following an episode of coma and shock, but he recovered and was discharged from the hospital without a specific diagnosis. In March 1960 he developed sudden severe cramping pains and paleness of both legs. Embolectomies were performed

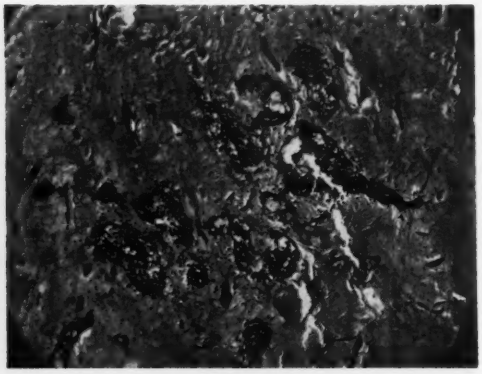

Figure 2

Center of the tumor showing vascular channels, stellate cells and multinucleated cells in an amorphorus stroma containing plasma cells and lymphocytes. Hematoxylin-eosin stain.

on the left popliteal and right common femoral arteries. The removed tissue was diagnosed as myxoma.

The patient was transferred to the University of California Medical Center with a diagnosis of intracardiac myxoma. On physical examination his blood pressure was 120/80 mm. Hg. Ventricular extrasytoles were fairly frequent, and a variable systolic and a short diastolic murmur were heard along the left sternal edge with splitting of the first and second sounds.

On March 25, 1960, a cardiotomy was performed through a right anterolateral thoracotomy with use of extracorporeal circulation. Before an incision was made in the left atrium, ventricular fibrillation was intentionally induced to prevent further embolization. When the atrium was opened, a villous gelatinous tumor, which apparently occupied nearly the entire atrium, immediately bulged through the incision. The tumor was extremely friable, had a jelly-like consistency, and fell apart as it was removed from its origin near the closed fossa ovalis. After closure of the atrium, the heart was initially defibrillated with ease, but reverted to ventricular fibrillation that resisted defibrillation. The electrocardiogram showed an ischemic pattern. The patient's condition gradually improved and regular rhythm occurred spontaneously after 76 minutes.

The postoperative electrocardiogram showed changes indicating myocardial injury. The patient recovered completely except for persistent electrocardiographic evidence of myocardial damage.

The emboli consisted of two white, partially translucent masses that measured 17 by 10 by 10 mm. and 14 by 11 by 7 mm. and contained small

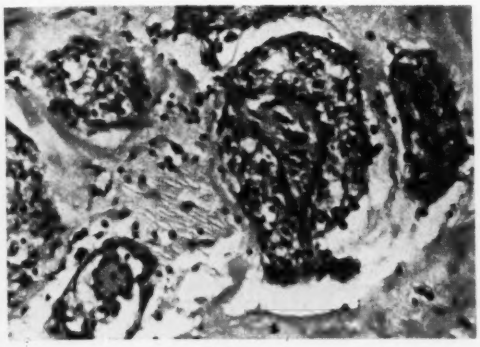

Figure 3

Vascular channels showing the thick wall of vacuolated material and stromal cells which are continuous with the endothelial cells lining the lumen. There are neutrophils and erythrocytes in the lumina, and plasma cells and lymphocytes in the stroma. Hematoxylin-eosin stain.

tan and brown areas. The specimen removed from the heart was composed of multiple pieces of lobulated, smooth, glistening, light yellow, partially translucent tissue that weighed 19.2 Gm. (fig. 4).

Microscopic sections showed masses of vacuolated light basophilic or, occasionally, light eosinophilic material whose papillary external surfaces were partially covered by numerous round and flattened cells (figs. 5 and 6). Within this loose stroma were scattered spindle-shaped, round and stellate cells that had round or oval nuclei and a small amount of eosinophilic cytoplasm (fig. 7). Many of the cells were multinucleated. No mitoses were seen. Also within the stroma were large areas of hemorrhage, masses of homogeneous eosinophilic material, and a few clumps of golden brown pigment. The few vascular channels in the stroma were lined by plump endothelial cells, occasionally several layers thick (fig. 8). The embolus contained small focal collections of neutrophils and the cardiac specimen contained small numbers of plasma cells and lymphocytes.

Incidence

Myxoma, the most frequent primary tumor of the heart, is a benign growth constituting nearly 50 per cent of all primary cardiac tumors.[3] In 1951, 128 myxomas were reviewed by Prichard,[3] and, in 1959, 90 additional cases were reviewed by Padhi and associates.[1] If Mahaim's case of a 3-month-old infant,[4] who probably did not have a myxoma, is excluded, the youngest reported cases are in

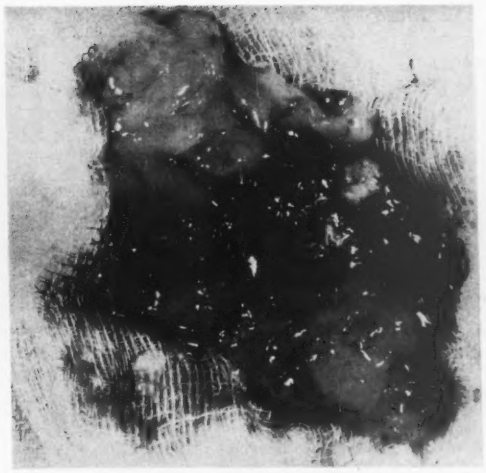

Figure 4

Myxoma of the left atrium showing its glistening lobulated external surface. It was very friable and gelatinous.

3-year-old children.[5, 6] McAllen[7] reported two patients, aged 72 and 73, and stated that Curtis[8] had reported the oldest case, that of an 83-year-old. The sex distribution has been reported both as being equal in men and women[3] and as being nearly three times more common in women.[7]

Etiology

The impression that myxomas are really thrombi seems to have arisen in several ways: (1) the failure to establish any criteria for myxoma or to distinguish between a myxoma and an obvious polypoid thrombus; (2) the rarity of the tumors and the inability of any one observer to amass a large experience with them; and (3) the presence in many myxomas of plump fibroblasts, hemosiderin, and large numbers of capillaries.[3] The last point deserves explanation. Myxoma is a soft tumor subjected to considerable mechanical stress; hemorrhages and hemosiderin deposition may be expected to occur from capillaries in such a structure. Likoff and associates,[9] in 1954, reported a pedunculated mass that arose near the foramen ovale and microscopically resembled a myxoma, but which he considered to be an organized thrombus.

Table 1

Successfully Removed Intracardiac Myxomas

Reported by	Year reported and date of operation	Age and sex	Chamber	Tumor size	Surgical method	How diagnosed and known time of survival
1. Crafoord	1955 7/16/54	45 F	Left atrium	?	Extracorporeal circulation	Angiocardiography; well 1 year later
2. Bigelow	1955 4/28/55	50 F	Left atrium	8 × 5 × 3½ cm. 75 Gm.	Hypothermia	Operation for mitral stenosis; well 3 years later
3. Scannell	1956 6/15/55	33 M	Left atrium	8½ × 3½ cm.	Hypothermia	Operation for mitral stenosis; well 5 months later
4. Bahnson	1957 4/3/56	57 F	Left atrium	6 × 5 × 4 cm.	Extracorporeal circulation	Operation for mitral stenosis; well 6 months later
5. Robertson	1957 6/21/56	38 F	Left atrium	6 × 6 × 6 cm.	Hypothermia	Operation for mitral stenosis; well 3 months later
6. Chin & Ross	1957 12/15/56	25 M	Left atrium	8 × 7 cm. 60 Gm.	Hypothermia	Operation for mitral stenosis; survived operation
7. Hanlon	1957 ?	61 F	Right atrium	?	Extracorporeal circulation	Angiocardiography; well 2 weeks later
8. Marions	1957 ?	?	Left atrium	4 × 4 × 4 cm.	?	Angiocardiography; survived operation
9. Fatti	1958 11/7/55	43 F	Left atrium	6 × 5 × 4 cm.	Closed	Operation for mitral stenosis; well 18 months later
10. Coates	1958 4/25/57	50 F	Right atrium	?	Extracorporeal circulation	Angiocardiography; well 6 months later
11. Gerbode	1958 5/16/57	51 F	Left atrium	42 Gm.	Extracorporeal circulation	Angiocardiography; survived operation
12. Belcher	1958 6/5/57	52 F	Left atrium	?	Hypothermia	Operation for mitral stenosis; survived operation
13. Krcilkova	1958 7/19/57	14 F	Right atrium	5½ × 5 × 4 cm.	Hypothermia	Fluoroscopy; well 4 months later
14. Krcilkova	1958 3/4/58	51 F	Left atrium	8 × 5 × 2½ cm. 52½ Gm.	Extracorporeal circulation	Angiocardiography; survived operation
15. Ellis	1958 ?	45 F	Left atrium	5 × 4 × 4 cm. 34 Gm.	Extracorporeal circulation	Operation for mitral stenosis; well 5 months later
16. Ellis	1958 ?	48 M	Right atrium	10 × 10 × 10 cm. 175 Gm.	Extracorporeal circulation	Operation for tricuspid stenosis; well 4½ months later
17. Malm	1958 ?	?	Left atrium	8 × 6 × 5 cm.	Extracorporeal circulation	Not reported
18. Hopkins	1958 ?	26 M	Right atrium	?	Hypothermia	Calcified on routine x-ray survived operation

Hopkins	?	M	atrium		Hypothermia	Calcified on routine X-ray survived operation
19.	1959	50	Left	5 × 5 × 5 cm.	Extracorporeal	Operation for mitral stenosis;
Cooley	6/25/57	M	atrium		circulation	well 1 year later
20.	1959	49	Left	?	Extracorporeal	Operation for mitral stenosis;
Cooley	9/25/57	F	atrium		circulation	well 18 days later
21.	1959	22	Left	158 Gm.	Hypothermia	Operation for mitral insufficiency;
Wittenstein	3/14/58	M	atrium			survived operation
22.	1959	48	Right	?	Extracorporeal	Cardiac catheterization;
Cooley	3/20/58	F	atrium		circulation	well 6 months later
23.	1959	47	Left	7 × 6 × 3½ cm.	Extracorporeal	Operation for mitral stenosis;
Deshmukh	10/4/58	F	atrium		circulation	well 6 months later
24.	1959	46	Right	9 × 5 cm.	Hypothermia	Angiocardiography;
Padhi	2/9/59	M	atrium	100 Gm.		well 6 weeks later
25.	1959	32	Left	7 × 6 × 3 cm.	Extracorporeal	Cardiac exploration for emboli;
Kay	2/10/59	F	ventricle		circulation	well 2 months later
26.	1959	38	Left	6 × 3 × 3 cm.	Hypothermia	Operation for mitral stenosis;
Collis	7/5/59	F	atrium			well 4½ months later
27.	1959	52	Left	?	Hypothermia	Angiocardiography;
Wittenstein	?	F	atrium			survived operation
28.	1960	51	Right	7 × 6 cm.	Extracorporeal	Angiocardiography;
Taber	4/25/57	F	atrium		circulation	well 8 weeks later
29.	1960	57	Left	28 Gm.	Hypothermia	Operation for mitral stenosis;
Aldridge	4/2/58	F	atrium			survived operation
30.	1960	38	Right	6 × 6 × 6 cm.	Extracorporeal	Angiocardiography;
Ashman	10/23/58	M	atrium		circulation	well 1½ months later
31.	1960	36	Left	7 × 4½ × 2½ cm.	Extracorporeal	Operation for mitral stenosis;
Barnard	10/28/60	M	atrium		circulation	well 3 weeks later
32.	1960	54	Right	10 × 8 × 4 cm.	Extracorporeal	Operation for tricuspid obstruction
Taber	7/21/59	F	atrium		circulation	well 6 months later
33.	1960	29	Left	?	Extracorporeal	Operation for mitral stenosis;
Solomon	7/29/59	F	atrium		circulation	well 6 months later
34.	1960	8	Left	3 × 3 × 2 cm.	Hypothermia	Embolectomy;
Beanlands	9/15/59	F	atrium			well 8 months later
35.	1960	54	Left	7½ × 5 cm.	Extracorporeal	Angiocardiography;
Michaud	9/17/59	M	atrium		circulation	well 3 weeks later
36.	1960	?	Left	?	Extracorporeal	Operation for mitral stenosis;
Fell	?		atrium		circulation	survived operation
Present	1960	55	Left	5 × 4 × 3 cm.	Closed	Operation for mitral stenosis;
case	2/18/60	F	atrium			well 3½ months later
Present	1960	12	Left	19.2 Gm.	Extracorporeal	Embolectomy;
case	3/25/60	M	atrium		circulation	well 2 months later

Percentage of females, 69 per cent; males, 31 per cent. Average age: females, 45 years; males, 35 years.
Percentage in left atrium, 71 per cent.
Seven additional cases have been reported.[81, 84-87]

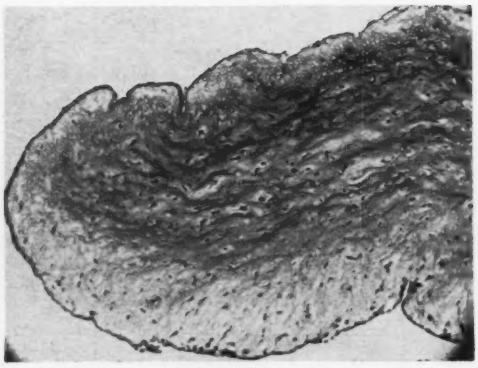

Figure 5

Characteristic myxoid stroma containing stellate and multinucleated cells. Plump endothelial cells cover the surface. Hematoxylin-eosin stain.

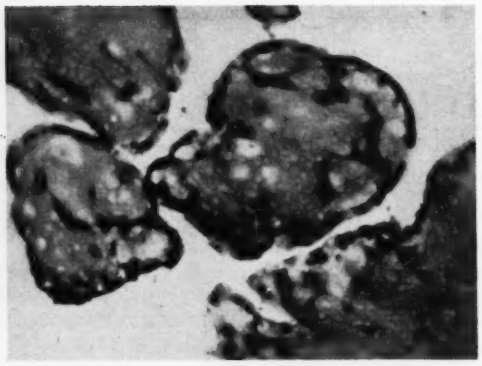

Figure 6

Surface endothelial cells continuous with stellate and multinucleated cells in an abundant myxoid matrix. Hematoxylin-eosin stain.

There are many sound reasons for considering the myxomas as true neoplasms. Most tumors are much larger than thrombi and are far less cellular. They do not retract in the fashion of thrombi elsewhere. They occur for the most part in hearts free from other disease. There is usually no evidence of damage to account for thrombosis. Almost all myxomas are found in the atria, especially the left, while thrombi occur with approximately equal frequency in the atria and ventricles. Most atrial thrombi are found in the atrial appendages but no myxomas have been found in this location. There are no convincing intermediate stages between a frank thrombus and a myxoma, even in the pedunculated and ball-valve thrombi found in the atria. There is no evidence of stratification in myxomas, although almost all thrombi are stratified. The position of elastic fibers along the peripheral free margin of these tumors is not observed in thrombi.[10] The presence of acid mucopolysaccharide within either thrombi or myxomas is not specific but indicates a particular type of mesenchymal tissue. Tissue cultures of myxomas grow both endothelial cells and fibroblasts.[11]

Ribbert[12] considered that the tumors arose from remnants of the myxoid tissue that compose the embryonic endocardium. In his experience the frequent persistence of such tissue around the fossa ovalis furnished an explanation for the peculiar localization of these tumors. It was apparent that there was more connective tissue within the interatrial septum than in any other part of the heart. More of this was in the flat left portion of the septum than in the indented right side. In a few cases small irregular areas of loose fibrillar connective tissue were present between the flaps of the foramen. In four cases the endocardium showed minute areas in which there were lacunae of capillary size lined by plump endothelial cells. Orr[13] suggested that the neoplastic part of the myxoma is the endothelial element and that the myxoid stroma is a degenerative phenomenon.

The mechanical stresses to which a soft tumor in a cardiac chamber is subjected are probably responsible for the tendency of these tumors to be myxoid.[3] In two cases reported by Prichard the myxoid areas were most prominent at the base and edges of the tumor, where motion is greatest. Although myxomas have been named for this myxoid tendency, the evidence indicates that it is of minor importance. Myxomas frequently contain areas in which the solid groups and cords of spindle-shaped and multinucleated cells in the stroma are continuous with similar cells lining vascular channels and with endothelial cells over the surface of the tumor (figs. 3, 6, and 8). Raeburn[14] regarded

the stroma cells as derivatives of fibroblasts and as precursors of endothelial cells, and stated that the tumors are essentially angiomatous.

These tumors should be distinguished from the so-called myxomas of the valves of the heart. Small collections of myxoid tissue are occasionally found in cardiac valves, especially in infants. These probably represent persistence of the embryonic stage when the valves were composed entirely of myxoid tissue. Such focal collections of myxomatous or loose connective tissue, in some instances referred to as Lambl's excrescences, were believed by Craig[15] to represent a form of endocardial fibroelastosis. Raeburn[16] reviewed these lesions and considered them fibroelastic hamartomas. Some lesions consist of villous processes covered by endothelium and arise from the valve cusps, generally the ventricular surface of the aortic and pulmonary valves and the atrial surface of the mitral and tricuspid valves.[16] The stroma is composed of collagen fibers and is surrounded by looser connective tissue that often appears myxomatous. These lesions may be distinguished from atrial myxomas by their location, small size (up to 1.5 cm.), lack of clinical significance, characteristic papillary structure, and often by their lack of vessels.[17] In addition these lesions fail to exhibit reactions for acid mucopolysaccharide, reactions commonly found in myxoma.[10] In the myxoma of a heart valve in a stillborn child reported by Reddy and co-workers,[18] the lesion was "the size of a pepper seed." The pseudomyxoma of the pulmonary valve in a newborn reported by Helwig[19] "showed a loose edematous stroma with very many young connective tissue and myxomatous cells buried in it."

A case reported by Fayen and Baglio,[20] which might be included in this group, was that of a patient with a polypoid mass, measuring 6 by 4 by 4 mm., found on the posterior papillary muscle of the left ventricle. The lesion was unusually cellular and similar cells were present in the adjacent myocardium. Abundant myxoid stroma, multinucleated cells, and plasma cells were absent. Another case, which probably does not belong in the myxoma group, was a 3-month-old girl reported by Mahaim.[4] A microscopic focus of myxomatous tissue was found in the membranous septum partially interrupting the bundle of His. Its microscopic size, location, intramural position, and lack of vascularity are not typical of myxomas.

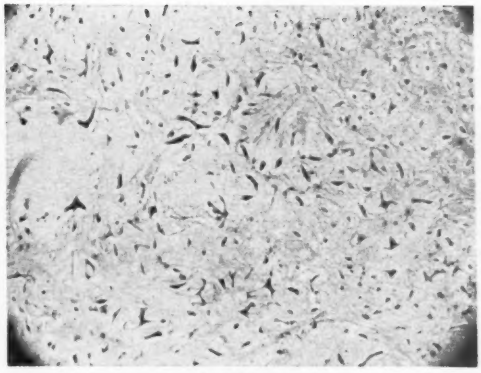

Figure 7

Spindle-shaped, stellate, and multinucleated cells in a myxoid matrix. Hematoxylin-eosin stain.

Gross Pathology

Myxomas are found almost exclusively in the atria; roughly 75 per cent occur in the left atrium. Their localization is even more specific in that almost all of them attach to, or overlie, the fossa ovalis or its rim. The tumors are generally solitary but cases of multicentric myxoma have been reported.[21–23] In one case,[23] multiple myxomatous nodules lay within the wall of the pulmonary artery. Three cases of myxomas arising in the left ventricle have been reported.[20, 24, 25] Most myxomas nearly filled the chamber and produced some degree of obstruction. Some of the atrial tumors extended into the ventricles. One myxoma was microscopic in size,[4] and a few have exceeded 10 cm. The tumors were entirely intracavitary except in one instance.[4] They are usually polypoid (80 per cent), are frequently pedunculated, and are externally glistening, smooth or gently lobular, often with polypoid projections. Occasionally they are villous. Their consistency varies with

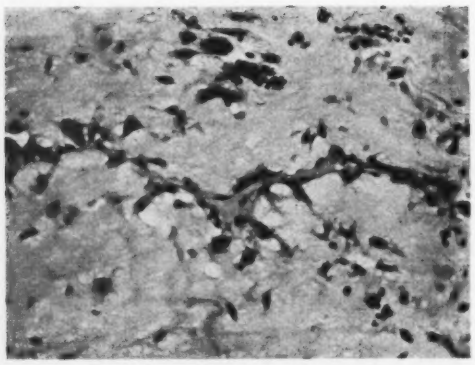

Figure 8

Small groups of stroma cells continuous with similar cells lining a vascular channel. Hematoxylin-eosin stain.

their collagen content, which has been variously described as gelatinous, soft, rubbery, firm, or resilient. The tumors are white, yellowish-white, yellow, or light brown and frequently display areas of hemorrhage. Thrombi sometimes overlie the surface of the tumor. The external surface may be indented where the growth has prolapsed through a valve orifice. The weight of the heart is usually normal or slightly increased, although several tumor-bearing hearts have weighed 700 to 800 Gm.

Microscopic Pathology

The average tumor is described as being poorly cellular, covered by endothelium, and composed of loose tissue of varying vascularity. Stellate, spindle-shaped, and multinucleated cells are scattered throughout. Mitoses are not seen. Most of the blood vessels are of capillary size, and their lining cells are plump and often multilayered. Larger vessels with thick walls may be present and are occasionally thrombosed. Hemorrhages into the stroma are common and hemosiderin is found in varying amounts, both free and in macrophages. Lymphocytes and plasma cells are almost always present, with occasional focal collections. Mucin stains are often positive in all or part of the matrix. The matrix is vividly colored by the Alcian blue and the Rinehart-Abul-Haj stains.[10] The Hale colloidal iron stain is also positive.[26] These reactions, which indicate the acid mucopolysaccharide nature of the matrix, are best visualized in sections prepared from alcohol-fixed tissue. They are usually negative in Zenker-fixed tissue, and only faintly positive in formalin-fixed tissue.[10] Calcification and bone formation are occasionally found in these tumors. Collagen deposition is variable. Stains for elastic tissue frequently reveal large numbers of elastic fibers focally or throughout the tumor. The elastic-fiber network of the endocardium has generally been described as intact, but in four cases reported by Raeburn[14] and one by Fisher and Hellstrom,[10] definite elastic laminae were demonstrated just beneath the surface of the tumor that were continuous with the atrial elastic fibers.

No evidence has been presented indicating that a significant number of these tumor-bearing hearts have been injured by a recognized process other than the primary one.

Symptoms

Symptoms result from cavitary obliteration, occlusion of the valve orifice, or arterial embolism. Obstruction of blood flow in the right or left atrium may cause dyspnea, cough, retrosternal pain, weakness, palpitation, arrhythmia, hemoptysis, cardiomegaly, or congestive heart failure.

In many cases no features could be elicited that would distinguish mitral stenosis caused by rheumatic heart disease from these intracardiac tumors. The intermittent valvular obstruction occasioned by the prolapse of the pedunculated and mobile polyp may be manifested by intermittent attacks of syncope, as episodes of paroxysmal dyspnea or by arrhythmias, dyspnea, pain, syncope, or changing heart murmurs associated with positional change.

Recurrent emboli, abdominal pain, fever, and evidence of peripheral emboli may suggest subacute bacterial endocarditis.[27, 28] In many cases a significant elevation of the sedimentation rate occurs.[29] Raynaud's phenomenon has been attributed to myxoma

emboli.[30] At autopsy bits of tumor emboli are often demonstrated in the heart, kidney, and spleen.[31] Emboli have also been reported in the brain,[23, 32–37] lungs,[38] aorta,[9, 25, 34, 39] renal arteries,[40, 41] central retinal artery,[42] and the extremities.[35, 43–45] Sudden death from pulmonary embolism caused by a myxoma of the right atrium has been reported.[38]

Diagnosis

By 1959 43 reports of confirmed diagnosis of myxoma during life were published, and in 27 of the 43 the tumor was encountered during surgical exploration.[1] If myxomas are kept in mind when these symptoms are present, a positive diagnosis can often be made. Refractoriness of the congestive failure may suggest the diagnosis. A history of rheumatic fever is usually not present with myxomas simulating mitral stenosis but patients with myxoma and a history of rheumatic fever have been reported.[28, 46] Myxoma and mitral stenosis have been found in the same patient.[47, 48] An opening snap is usually absent but may occur.[49, 50] Phonocardiography will confirm its absence or presence. Mitral insufficiency has been diagnosed on the basis of right-sided and left-sided heart catheterization.[51] A feature that may make the diagnosis possible is alteration of the symptoms when the patient changes his position. There may be roentgenographic evidence of interstitial pulmonary fibrosis[52] or calcium within the tumor.[53] Murmurs may rapidly appear or disappear, or change in quality or intensity. In cases simulating subacute bacterial endocarditis, splenomegaly, petechiae, and positive blood cultures will not be present. Microscopic examination of tumor emboli will often permit a diagnosis.[40, 44, 54] Embolization in rheumatic heart disease is unusual without atrial fibrillation. Isolated tricuspid stenosis is rare in rheumatic heart disease and should suggest right atrial tumor. Right atrial myxomas may be confused with Ebstein's malformation of the tricuspid valve or constrictive pericarditis.

Once an intracardiac tumor is suspected, angiocardiography may confirm the diagnosis.[6, 55] Some tumors, however, are not demonstrated by this procedure. Myxomas must be differentiated from thrombi. Myxomas usually are not attached to the posterior wall of the left atrium and produce no filling defects in that region. The attachment of the myxoma near the fossa ovalis may be seen. Left atrial thrombosis is suggested by finding irregular margination of the junction of the left atrial appendage with the left atrium and sparse or no visualization of the left appendage.[56] Van Buchem,[55] using fluoroscopy, thought that a strong pulsatory movement of the esophagus at the level of the left atrium, synchronous with the left ventricular action, was of diagnostic significance.

Treatment

In 1942 Beck[57] reported the first successful removal of a cardiac tumor. Other tumors that presented on the external surface of the heart subsequently have been partially or completely excised.[58–61]

Attempts were made to remove cardiac tumors with the aid of hypothermia. These maneuvers were generally unsuccessful because the limitations of time, exposure, or ventricular fibrillation did not permit removal of the mass.[55, 62–65] In 1955 Bigelow[66] successfully removed a left atrial myxoma using hypothermia. At least 12 additional cases in which hypothermia was used were managed successfully.[1, 26, 44, 46, 47, 49, 51, 53, 67–69]

In 1954 the development of the pump-oxygenator led Clowes and associates[70] to remove a left atrial tumor, but the patient died 6 hours postoperatively. In March 1955, Crafoord[2] described the successful removal of a left atrial myxoma. In April 1956, Bahnson et al.[71] reported that they had successfully removed a left atrial myxoma with the use of a pump-oxygenator system. At least 20 additional cases have been reported of successful removal using a pump-oxygenator system.[11, 24, 43, 52, 69, 72–82] Eleven reports have been published of successful removal of right atrial myxomas[1, 53, 69, 72, 74–76, 78, 79, 81] and one of a left ventricular myxoma.[24]

In April 1955, Nichols[64] became the first surgeon to remove an atrial myxoma using a closed method. He inserted a snare, with a net attached to it, through a purse-string atrial appendage. Because of the size of the tumor it could not be entirely removed during the first attempt, and the instrument broke before complete removal could be performed. In 1958 Fatti[83] reported successful removal of a myxoma by a closed approach. He placed the index finger of one hand into a purse-string opening in the anterior wall of the left ventricle and the index finger of the opposite hand through a similar opening in the left atrium. He was able to deliver the tumor through the atrial opening.

Intracavitary myxomas should be treated by surgical removal, which can be carried out safely only with the aid of inflow occlusion. Closed methods are dangerous, since many of these tumors are very friable. In addition, blood loss is often considerable if the opening is large enough to permit delivery of the tumor, and it is not always possible to remove the tumor completely. It is important that the atrium and ventricle be searched carefully before normal circulation is resumed. Adequate time for this is assured by the use of extracorporeal circulation. When a myxoma is encountered during a proposed operation upon the mitral or tricuspid valve, it is seldom justified to attempt to remove it by a closed method. When circumstances make it necessary to do so, the hazards of embolization and exsanguination can be reduced by temporary, induced ventricular fibrillation to arrest the circulation.

Discussion

Both of the cases presented in this paper are good examples of how easily fragments of the tumor, or the entire tumor, may become detached, and why an open procedure is recommended. Fortunately the tumor was of a firm consistency in our first case so that embolization did not occur during its manipulation. Many other attempted removals without the aid of cardiac bypass or hypothermia have been unsuccessful and our first case is only the second successful complete removal by a closed method. Had it not been for the development of ventricular fibrillation, which arrested the circulation, it is probable that the massive hemorrhage could not have been controlled.

In our second case, the patient was the third child to have an intracardiac myxoma removed successfully, and the second successful case to be diagnosed by recovery of a peripheral embolus. Previously an 8-year-old girl had a myxoma successfully removed following recovery of a myxoma embolus.[44] These cases demonstrate the importance of sectioning emboli routinely. We believe that the deliberately induced ventricular fibrillation prevented serious embolization of the huge, extremely friable, soft mass which was very difficult to evacuate from the atrium.

Summary

A comprehensive review of the various aspects of intracardiac myxomas is presented. Two unusual cases are illustrative of many of the problems encountered. Of particular interest are the successful surgical removals of the myxomas in both cases.

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Every author contrives, I believe, to persuade himself that the work which consumes his own midnight oil, is precisely the one that is wanted. It is for the reader to determine whether I labour under the delusion common to my brethren.—J. Hope, M.D. *Diseases of the Heart and Great Vessels.* London, William Kidd, 1832, p. 10.

BOOK REVIEWS

Oxymetrie. Theorie und klinische Anwendung. *Kr. K. Kramer.* Stuttgart, Georg Thieme Verlag, 1960, 208 pages, 154 figures. $9.40

The volume presents a collection of 23 papers delivered at an oximetry symposium in Bremen, Germany, in 1959. The contributors discuss some theoretical, technical, and clinical aspects of oximetry including not only measurements of SO_2, but also photoelectric plethysmography and certain clinical aspects of dye-dilution curves. Of interest are the papers by Zijlstra on reflection oximetry, a method that uses photoelectric recording of reflected rather than transmitted light. The method is independent of hemoglobin concentrations, but in the present form is sensitive to rouleaux formation of red cells, and may be used as a quantitative estimate for the latter. A report by Bender on the use of a catheter-tip oximeter may point the way toward a study on the influence of catheters and of the vascular bed upon the shape of indicator-dilution curves. Most presentations, however, are not particularly original, and many important basic problems of instrumentation, technic, and interpretation are barely touched upon. For the American reader, therefore, the volume contains little of sustained interest.

HANS H. HECHT, M.D.

Bedside Medicine. *I. Snapper.* New York, Grune & Stratton, Inc., 1960, 592 pages. $14.50.

As the title implies, the author emphatically affirms that the true physician must be oriented not to the laboratory but to the bedside and, presumably, to the nearby reclining patient. As he states in his introduction, "Since lip service is still paid to the fame of Hippocrates, this great teacher's concepts of medicine in general, of the practice of bedside medicine in particular, may be quoted here. Hippocrates taught that the greater part of the medical knowledge which the physician must apply *at the bedside* is based on profound experience in the *practice* of medicine and clear logical reasoning about cause and effect. At the same time, the physician must not only possess a wide knowledge of the natural sciences, he must also devote considerable time to study and experimentation in these basic fields. However, at the bedside, the Hippocratic physician is forbidden to indulge in theoretic discussions and generalized theorizing. Finally, an ethical concept based on an elevated moral law is indispensable . . ."

The author then continues "In contrast to these Hippocratic aphorisms the modern medical scions do not respect the empirical knowledge which is necessary for diagnosis and therapy: Their interest has been captivated almost exclusively by the study of animal experiments and the investigation of complicated laboratory methods."

In this book the author, in an almost conversational style, states that this volume contains "a record of the medical knowledge I have acquired by experience in combination with the modicum of natural sciences which is necessary to the practice of good medicine. This book, therefore, is a discussion of bedside medicine—as I like it. I am fully aware that other clinicians prefer a completely different type of bedside medicine."

The book contains 17 chapters, each one of which reflects the astute, sharp clinical acumen of the author. The chapters do not follow the usual textbook organization of definition, etiology, pathology, clinical pathology, diagnosis, and treatment. Indeed, there are few subheadings in the entire volume. Nor does the author attempt to give a comprehensive dissertation on the various diseases with references to the literature. This book, therefore, in no way competes with the usual textbooks for undergraduates and graduates, nor is it sufficiently comprehensive to serve as a volume for ultimate reference. It does provide, however, a wholly pleasant, almost interpersonal relationship, with a highly able clinician who interweaves many delightful references to his experiences in the Orient. Internists will probably disagree with some of the author's views and find coverage of some of the subjects inadequate. But almost all will surely enjoy the salty discourse and incisive comment.

HERRMAN L. BLUMGART, M.D.

Introduction to a Submolecular Biology. *Albert Szent-Gyorgyi.* New York & London, Academic Press, 1960, 135 pages.

This small volume presents a stimulating, informative, and speculative query into the subject of the fundamental mechanisms involved in the energy exchanges associated with chemical reactions of metabolic pathways. Finding formal biochemistry inadequate to explain such problems as conversion of potential chemical energy into kinetic energy of muscle contraction, Dr. Szent-Gyorgyi turned to consideration of the details of electron interactions that underlie chemical reactions. Data obtained from such technics as magnetic electron resonance spectra, light absorption spectra, fluo-

rescence spectral analysis, etc., provide the clues to important energy changes involved in electron orbital shifts, partial electron charge transfers, pi-electron field charge. A fundamental observation is made that only relatively small energy exchanges appear to be compatible with chemical reactions that form the basis for living structures. In its attempt to bridge the gap between the nonliving and the living, Dr. Szent-Gyorgyi's essay is a lineal descendant of Schrodinger's famous Dublin lectures entitled "What Is Life." The concepts and orientation of "submolecular biology" will undoubtedly occupy a more and more important role in the development of biochemistry.

HERBERT A. RAVIN, M.D.

Atrial Septal Defect: An Investigation into the Natural History of a Congenital Heart Disease. *H. Gosta Davidsen.* Copenhagen, Denmark, Munksgaard, 1960, 225 pages, Illustrated. D. Krone 50.-

This book, a comprehensive treatise on the subject of atrial septal defect, reviews in considerable detail both the clinical and basic embryologic, anatomic, radiologic, and electrocardiographic aspects of the condition.

The clinical and hemodynamic data, as well as much of the radiologic information, are based on studies carried out by the author and his associates, whereas the analysis of the pathologic anatomy and embryology is on the basis of extensive studies of the literature. In this scholarly presentation, the author has covered all available theories regarding the anatomic and embryologic configuration of the various defects stressing those that he thinks are most probable. In addition to the basic anatomy, embryology, and hemodynamic presentation, there is a superb clinical section, which should be useful either as an introduction to this subject or for review of the physiologic and diagnostic problems associated with interatrial septal defects.

This extensive and yet not excessively erudite manuscript comes at a time in the course of the clinical management of this condition when many who have been intimately involved with its therapeutic aspects over the past few years may be ready for a review of the basic anatomic and physiologic facts, so that they may better evaluate the efficacy of their treatment thus far.

SAMUEL R. SCHUSTER, M.D.

Cardiac Emergencies and Related Disorders: Their Mechanism, Recognition, and Management. *Harold D. Levine.* New York, Landsberger Medical Books, 1960, 381 pages, 44 figures. $12.00.

In the opinion of the reviewer, this book should be carefully studied and kept available for ready reference by all physicians who have, or may have, the responsibility for the care of cardiac patients. The author has had many years of experience in the field covered by this volume, which he describes as the outgrowth of a series of seminars presented during the last 15 years to fourth-year students of the Harvard Medical School. In a charmingly modest preface, the author expresses the belief that this monograph represents "a synthesis of the mainstream of medical thinking at the Peter Bent Brigham Hospital, of my own experience, and of what reading I have managed to do."

The seventeen chapters include not only the dramatic, sudden emergencies such as acute myocardial infarction, acute left ventricular failure, pulmonary embolism, paroxysmal ventricular tachycardia, and syncope, but also a number of others that might not readily come to mind. These include digitalis intoxication, refractory congestive heart failure, atrial fibrillation, atrial tachycardia with block, and a number of noncardiac conditions. The chapter entitled "Unusual and Non-Cardiac Causes of Chest Pain" contains a brief, lucid, helpful discussion of 10 conditions that may simulate the chest pain of acute myocardial infarction.

To say that this volume measures up to the expectations of those who have known Dr. Levine, and who have profited by reading his many excellent papers, is to bestow high praise. It is comprehensive, practical, and written with great clarity. The numerous illustrations have been chosen with care and reproduced beautifully. Each chapter is followed by a list of important references, the number ranging from 2 to 53. With refreshing candor and honesty the author confesses that familiarity with all the literature on the subject of emergencies is quite impossible. "Each contribution read brings to light in geometrical progression a growing avalanche of additional references. As a practising physician it would have been impossible for me to read them all."

This small volume has been read with pleasure, admiration, and profit. It is commended without reservation to all who may encounter cardiac emergencies. I think there are few whose confidence and effectiveness would not be increased by a careful reading of these sane, helpful comments, which constantly reveal the experience, wisdom, and sound judgment of the author.

H. M. MARVIN, M.D.

The Heart in Industry. By Twenty-Four Authors, Edited by *Leon J. Warshaw.* Paul B. Hoeber, Inc. Publisher, 1960, 659 pages. $16.00.

This volume presents a relatively unique and comprehensive symposium on the general subject of heart disease in relation to employment by a panel of twenty-four recognized authorities. It should prove of special value for general reading

and as a reference to the industrial physician or surgeon. Also it should be of interest to the internist or cardiologist who is concerned with rehabilitation and employment of the heart patient, or who may become ensnared in the intricacies of workmen's compensation claims. For the general practitioner it will be valuable in giving a review of important basic concepts of cardiac physiology, rehabilitation, and even therapeutic management of certain conditions; furthermore, it emphasizes the relation of family physician to the industrial physician, pointing out the necessity of understanding cooperation for the best interest of the patient. Reading and study of materials presented should lead to furtherance of intelligent rehabilitation and employment of heart patients.

The Physiologic Effect of Work on the Heart is discussed in an interesting and practical manner with emphasis on work load and heat or environmental factors.

The chapter on Detection and Evaluation of Heart Disease is a review of what may be found in most texts on heart disease. Of importance is emphasis on fact that stress tests are not always practical and do not necessarily correlate with ability to perform on the job.

The problem of Mass Screening for Heart Disease is interestingly discussed with presentation of an attractive program for industry.

The chapters on Selective Placement and Vocational Rehabilitation give a comprehensive review of these subjects with a full description of the cardiac work classification unit and concepts developed therefrom. Practical considerations of sheltered workshops, union attitudes, and the roles of useful agencies are stressed. Actually the contents of these chapters somewhat overlap and they might well have been combined.

The chapter on Industrial Aspects of Non-occupational Heart Disease devotes some 72 pages to an excellent résumé of common cardiac conditions and present-day concepts of handling, but most of this material is likewise readily available in a modern text of cardiology. There is further reduplication in discussion of rehabilitation principles and evaluation for work.

Psychiatric Aspects of Cardiovascular Disease in Industry are well set forth. The reviewer was a bit startled by the statement that certain cardiovascular diseases, including coronary heart disease and hypertensive heart disease, are classed as psychosomatic disorders; also in discussion of coronary disease by the statement, "Virtually all the elements in current theories of its pathogenesis have been shown to be evoked by stress." Of significance is the statement, "The physician must sometimes choose either the organic heart disease or the cardiac neurosis as the primary target for his treatment."

The chapter on Cardiac Emergencies is well presented with clear tabular presentations, especially of the arrhythmias. The dilemma of emergency thoracotomy and cardiac massage might have been better resolved through discussion of external cardiac massage, but presumably the chapter was written before the advent of this recently recommended procedure, which could be quite applicable to the industrial emergency. It is surprising that *cedilanid* was not included as a parenteral emergency digitalis preparation of choice. Many would favor omission of *mecholyl* as an emergency room therapy for paroxysmal tachycardia.

Peripheral Vascular Diseases are discussed in a refreshingly concise and complete manner with important observations on medicolegal and disability aspects, which have rarely received deserved consideration in the past.

The chapter on Vehicle Operation and Aviation is a most important and controversial subject with reasonable conclusions drawn. The differences between private and commercial transport are stressed. The portion on aviation opens new avenues of thought. The statement, "Only five of the commercial airlines have their own medical programs and examine pilots regularly," and that those rejected have "little difficulty in getting jobs with the other airlines," was most shocking and provocative.

The chapter on The Cardiac on the Farm, while not a subject of wide interest, presents many valuable and interesting concepts regarding work simplification, and the philosophy and psychology of work which make it of importance to all.

The section on Cardiovascular Effect of Toxic Occupational Exposures gives a wide review of a subject not usually considered in relation to heart disease, but one of special importance in creating a further awareness of its implications in spite of their relative infrequency. The discussion of carbon monoxide intoxication is noteworthy. This is a valuable reference section.

Cor Pulmonale and Industrial Lung Disease is concisely and clearly set forth, including an excellent outline of treatment for cardiorespiratory failure.

The subject of Traumatic Heart Disease is well portrayed with illustrations.

Stress, Physical Activity, and Coronary Artery Disease in its various phases is interestingly presented in light of our present limited knowledge. In contradistinction to the statement in the chapter on psychiatric aspects, here we read, "There is no current scientific basis for the impression held by some clinicians that mental stress or emotional disturbance enhances or accelerates the atherosclerotic process."

Next comes the discussion of Workmen's Compensation and Heart Disease. The history of compensation and the well-known dilemmas of the problem are reviewed with illustrative cases; also some of the suggested aids toward solution.

There is a final chapter on Health Education in Industry.

To one versed in this entire subject of the heart in industry the text adds relatively little new to the existing literature but serves an important purpose in drawing diverse material together in an interesting sequence. Improvement might be made in condensation of portions, deletion of certain basic material well set forth in ordinary texts, and avoidance of repetition in certain sections. References, while not presenting a complete bibliography, are good and quite adequate. The format is pleasing, and the indexing quite complete. This book should prove a valuable addition to all medical libraries.

RICHARD J. CLARK, M.D.

Leukaemia: Research and Clinical Practice. *F. G. J. Hayhoe.* Boston, Little, Brown and Company 1960, 335 pages, 53 figures. $16.00.

The need for a monograph on leukemia in the English language was filled within the last 2 years by Dameshek and Gunz's book, and more recently by the one presently reviewed. Both these books cover the subject in an excellent manner, although the emphasis differs. Hayhoe's accent is on the chemical and experimental aspects of this disease. A detailed description of negative experimental and metabolic findings makes the reading of some chapters cumbersome, but may be welcomed by certain investigators. The author repeatedly expresses sharp criticism in his appraisal of experimental findings and opinions on diverse aspects of leukemia. The excellence of the chapters "The Incidence and Ecology of Leukemia in Man" and "Cytology and Chemistry" is commendable, although description of the cytochemical technics discussed is missing.

The placing of the chapter on therapy before that on the clinical aspects of leukemia is not justified. The plates are excellent, but some legends are incomplete and do not specify whether the cells are from peripheral blood or bone marrow; only perusal of the text clarifies the origin of some of them. This book is especially recommended for the reader interested in the theoretical and laboratory aspects of leukemia.

LIBERTO PECHET, M.D.

Valvular Disease of the Heart in Old Age. *P. D. Bedford* and *F. I. Caird.* Boston, Little, Brown and Company, 1960, 194 pages, 38 Illustrations. $7.50.

The medical triumphs of the twentieth century have extended the average lifespan considerably. Increasingly, the practice of all physicians, particularly cardiologists, must be directed at the care of the aged. Thus, there is considerable interest in this little monograph based upon in-patients under the personal care of the authors at the Geriatric Unit, Cowley Road Hospital, Oxford. In the light of their personal experience they have attempted to define the incidence, clinical manifestations, diagnosis, complications, and prognosis of the main forms of valvular disease with special reference to sources of error in diagnosis and to differences between the features of valvular disease as encountered in the young, the middle-aged, and in the aged. This type of study is of particular value, for it allows certain inferences to be made about the natural history of valvular disease in both the young and the aged, and, in a respectable number of the authors' cases, these inferences were subjected to proof at postmortem examination. It is of interest that they found no evidence that acute rheumatism as experienced by patients surviving to old age is substantially different from that seen in younger patients. Certainly rheumatic heart disease is by no means uncommon in the aged; on the other hand, the study of a small group of elderly patients with rheumatoid arthritis suggests that the association with clinically demonstrable rheumatic heart disease is more than can be explained by chance. In reviewing each of the common valvular deformities, a careful analysis of the physical findings and their significance has been made. Thus, in elderly patients an opening snap is rarely heard even in severe mitral stenosis, in striking contrast to its great frequency in younger patients. Moreover, the degree of mitral stenosis found post mortem is often severe; thus, the survival of these patients into later life and even into extreme old age requires explanation, which the authors think may be found in the gradual decline in cardiac output that occurs with advancing years. Two lesions that have evoked considerable interest among clinicians are thoroughly reviewed. Stenosis of the aortic valve is oftentimes difficult to differentiate from other causes of systolic murmurs in the aged. Similarly, isolated aortic incompetence often presents a difficult differential: the authors deal with this subject exhaustively. The book is well printed with clear, easily read type, sharply delineated tables, and carefully chosen photographs of pathologic specimens which are very helpful. This small volume will be read with profit by all those interested in diseases of the heart and by physicians interested in the aged.

GEORGE S. KURLAND, M.D.

Bleeding Syndromes—A Clinical Manual. *Oscar D. Ratnoff.* Springfield, Illinois, Charles C Thomas, Publisher, 1960, 287 pages, Illustrated.

This excellent book covers a subject that the clinician too often avoids. Its success in making it alive and clear, will hopefully change this attitude. Written for the nonspecialist, every effort is made to facilitate his understanding and interest. Although the clotting and bleeding mechanisms involve more and more understanding of biochemistry, the author avoids going into biochemical and, indeed, theoretical discussion as much as possible. One of the purposes of this book is supposed to be the elimination of the complex terminology indiscriminately used in the literature. To this same purpose, the International Committee for the Nomenclature of Blood Clotting Factors decided to use Roman Numbers for the accepted clotting factors. This is becoming increasingly used in the literature. Although the author presents a comprehensive list of synonyms for the clotting factors his preference for some terms, like Pro-Accelerin for Factor V or Pro-S PCA for Factor VII throughout the text contributes to maintain the present confusion, especially for the nonspecialist.

The discussion, Diagnostic Considerations, is comprehensive but the actual description of the technics used by Dr. Ratnoff might have been a valuable contribution to this book.

The bibliography is very comprehensive (731 references) and up-to-date. It offers a broad choice for the reader interested in a particular subject.

The author's broad experience, both clinical and investigative, his candid sincerity on the unknown aspects in this field, and his particular talent as a writer, make the reading of this book a really enjoyable and enlightening experience.

LIBERTO PECHET, M.D.

BOOKS RECEIVED

CIRCULATION is very glad to acknowledge the receipt of the following books. Insofar as space permits, as many appropriate books as possible will be reviewed.

Clinical Vectorcardiography and Electrocardiography. *Edward Massie* and *Thomas J. Walsh.* Chicago, Illinois, The Year Book Publishers, Inc., 1960, 592 pages, 471 figures. $27.50.

Blood Flow in Arteries. *Donald A. McDonald.* Baltimore, The Williams & Wilkins Company, 1960, 328 pages, Illustrated. $8.50.

Der Akute Arterienverschluss Der Extremitäten. Diagnose und Therapie. *A. Kappert.* Stuttgart, Hans Huber, 1960, Illustrated. DM 34.—.

Clinical Applications of Cardiopulmonary Physiology. *M. Henry Williams, Jr.,* New York, Paul B. Hoeber, Inc., Medical Division of Harper & Brothers, 1960, 233 pages, 27 figures. $7.50.

Nature of Rheumatic Heart Disease: With special reference to Myocardial Disease and Heart Failure. *George E. Murphy.* Baltimore, The Williams & Wilkins Company, 1960, 289 pages, 162 Illustrations. $3.50.

Surgery of the Aorta and Its Branches. *James D. Hardy.* Philadelphia, J. B. Lippincott Company, 1960, 386 pages, 75 Illustrations. $6.50.

Congenital Malformations of the Heart. Vol. I. General Considerations. *Helen B. Taussig.* Cambridge, Published for the Commonwealth Fund by the Harvard University Press, 1960, 204 pages, Illustrated. $4.75.

Congenital Malformations of the Heart. Vol. II. Specific Malformations. *Helen B. Taussig.* Cambridge, Published for the Commonwealth Fund by the Harvard University Press, 1960, 1049 pages, Illustrated. $17.50.

Cardiac Disease in Pregnancy: Medical Care, Cardiovascular Surgery and Obstetric Management as Related to Maternal and Fetal Welfare. *Curtis Lester Mendelson.* Philadelphia, F. A. Davis Company, 1960, 385 pages, 141 figures and 68 tables.

Regulation of the Inorganic Ion Content of Cells. Ciba Foundation Study Group No. 5 In honour of Prof. E. J. Conway. Edited by *G. E. W. Wolstenholme* and *Cecelia M. O'Connor.* Boston, Little, Brown and Company, 1960, 100 pages, 16 Illustrations.

Resuscitation of the Newborn Infant: Principles and Practice. Edited by *Harold Abramson.* St. Louis, The C. V. Mosby Company, 1960, 274 pages, Illustrated. $10.00.

Heart Sounds and Murmurs: A Clinical Phonocardiographic Study. *P. A. Ongley, Howard B. Sprague, M. B. Rappaport,* and *A. S. Nadas.* New York, Grune & Stratton, Inc., 1960, 316 pages, Illustrated. $9.75.

Quantitative Vectorelectrocardiography. *Louis Brinberg.* Library of Congress No. 60-125-14. Baltimore, Waverly Press, Inc., 123 pages, Illustrated. $5.25.

Contribuicao Vectorcardiográfica para o Estude Das Hipertrofias Ventriculares. *Fernando de Padua,* Lisboa, Gazeta Medica Portuguesa, 1959, 481 pages, Illustrated.

Clinical Disorders of the Pulmonary Circulation. Edited by *Raymond Daley, John F. Goodwin,* and *Robert E. Steiner.* Boston, Little, Brown and Company, 1960, 364 pages, 133 Illustrations. $8.50.

Haemopoiesis: Cell Production and Its Regulation. Ciba Foundation Symposium. Edited by *G. E. W. Wolstenholme* and *Maeve O'Connor.* Boston, Little, Brown and Company, 1960, 490 pages, 107 Illustrations. $11.00.

Bleeding Syndromes—A Clinical Manual. *Oscar D. Ratnoff.* Springfield, Illinois, Charles C Thomas, Publisher, 287 pages.

The Johnson Recording Oscillometer. Its Use in the Study of Arterial Circulation. *Carl A. Johnson,* New York, Pergamon Press, 1959, 112 pages, 71 figures. $5.00.

ABSTRACTS

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ATHEROSCLEROSIS

Clarke, N. E., Sr., Clarke, N. E., Jr., and Mosher, R. E.: Treatment of Occlusive Vascular Disease with Disodium Ethylene Diamine Tetraacetic Acid (EDTA). Am. J. M. Sc. **239**: 732 (June), 1960.

Arguments are presented against the importance of fat and cholesterol in the pathogenesis of atherosclerosis and in support of a biological aging process stressing the importance of trace elements, calcium, and magnesium. Chelation of calcium and other minerals in the human body was attempted in the hope of alleviating the manifestations of occlusive vascular disease. EDTA (disodium ethylene diamine tetraacetic acid) was administered as follows: 3 Gm. in 500 ml. of 5 per cent glucose or normal saline was given intravenously over a 2- to 3-hour period. This was administered on each of five consecutive days each week. There were two series of infusions of 15 each with a rest period of 1 week between them. In addition, pyridoxine, 25 mg. three times daily was also administered during the period of the infusions. Short booster series of five daily infusions were given at intervals from 6 to 12 months. This therapy was given to 76 patients with angina pectoris (some of whom had had myocardial infarction), to 31 patients with intermittent claudication, rest pain, and pre-gangrene; and to 25 patients with cerebrovascular disease (including senility and tinnitus). Spectacular improvement was found in all three groups. With the exception of references to large series in the literature, no controls were utilized. The authors mention that the double-blind test is "far from infallible" and, with this, they dismiss comparative statistical analyses. In addition it was found that this therapy also produced prolonged lowering of the serum cholesterol.

SHEPS

Herdenstam, C. G.: Serum Polyunsaturated Fatty Acids in Coronary Heart Disease. Acta med. scandinav. **166**: 475, 1960.

It has been suggested that the development of atherosclerosis may be related to a relative deficiency of polyunsaturated fatty acids (PUFA) in the diet. UV-spectrophotometric analyses were made to determine the amounts of PUFA in the serum of 30 normal Caucasian subjects, 6 normal Japanese subjects, and 30 patients with coronary heart disease. There was no significant difference between the average serum level of the different polyunsaturated fatty acids expressed as a percentage of total lipids in the coronary group and in the controls. Among the Japanese, however, there was a significantly lower triene level, but otherwise the same amount of PUFA and total lipids as in the normal material. The author suggests that this may be related to a higher proportion of unsaturated fat in the diet of the Japanese. These data do not confirm the hypothesis that deficiency of PUFA in the serum is a factor in the genesis of coronary heart disease. The PUFA level in the serum may be in a dynamic equilibrium and regulated by homeostatic mechanisms.

SHEPS

Lukomsky, P. E., Bobkova, B. I., and Savenkov, P. M. The Administration of Unsaturated Fatty Acids in Patients with Coronary Atherosclerosis. Cor et Vasa 1: 100, 1959.

Forty patients with coronary arteriosclerosis were given 20 ml. per day (total dose 400 ml.) of linetol (a mixture of fatty acids of linseed oil), as a supplement to a basic diet of 2,400 calories containing 55 to 60 Gm. of fat., for 20 days. Serum cholesterol, beta-globulin, and beta-lipoprotein fractions showed a significant lowering, while the phospholipid cholesterol coefficient and albumins showed an increase. The only side effects were loose stools in five patients. These results encourage the prophylactic and therapeutic use of linetol in coronary arteriosclerosis.

LEPESCHKIN

Maurukas, J., and Thomas, R. G.: Treatment of Experimental Atherosclerosis in the Rabbit with L, D. Alpha (Dimyristoyl) Lecithin. J. Lab. & Clin. Med. 56: 30 (July), 1960.

Fifteen male rabbits were used. Five, as controls, were fed only regular Purina rabbit chow. At autopsy these animals showed aortas that were complete free of arteriosclerotic change. This finding was confirmed by histologic examination. Atherosclerosis was induced in the other 10 animals by feeding them high-cholesterol rabbit chow for 11 weeks. Then five of the atherosclerotic rabbits received infusions of synthetic L, D. alpha (dimyristoyl) lecithin through cannulated external jugular veins, at the rate of 100 ml. of 0.8 per cent of the emulsion over a 4-hour period. This infusion was repeated at intervals of 4 to 6 days. Two rabbits received five infusions; another received four; and two others, three infusions each. Blood samples before and at intervals after infusion were analyzed for total cholesterol, phospholipid phosphorus, and hematocrit. After a rest of 6 to 12 days, the 10 rabbits were killed, and their aortas were examined grossly and microscopically to estimate the degree of atherosclerosis. The remaining portions of the aortas were dried and analyzed for cholesterol, phospholipid phosphorus, and total fat content. Typical atherosclerotic plaques covered 50 per cent of the intimal surface of the aortas in five non-infused rabbits, reaching nearly 90 per cent in the arches. No plaques were found in one rabbit that had received five infusions of lecithin and the vessel walls appeared normal. Striking resolution of the plaques occurred in the second rabbit that had five infusions. The other infused rabbits showed some resolution. A gradual rise in plasma cholesterol and phospholipid phosphorus and a significant drop in hematocrit value were noted after administration of the emulsion. No striking difference was noted between the cholesterol content of lecithin-treated rabbit aortas and atherosclerotic control rabbit aortas.

MAXWELL

Sellers, E. A., and Baker, D. G.: Coronary Atherosclerosis in Rats Exposed to Cold. Canad. M. A. J. 83: 6 (July 2), 1960.

The development of coronary artery lesions was observed histologically in groups of rats fed various rations and maintained at 1 to 3 C. or at 22 to 25 C. for periods up to 82 weeks. Coronary lesions were not found in rats consuming a semisynthetic feed containing 10 per cent fat kept for 76 weeks at room or cold temperature. Lesions consisting principally of subintimal lipid deposition were noted in 5 per cent of rats eating a 34 per cent-fat feed in the cold, and in 16 per cent kept at room temperature. When 2 per cent of cholesterol had been added to a high-fat diet, the extent of coronary lipidosis increased and the incidence rose to 21 per cent of rats at room temperature and to 50 per cent of those at 1 to 3 C. In another experiment rats receiving a commercial ration had a coronary lesion incidence of 12 per cent when living at 22 to 25 C. and 59 per cent at 1 to 3 C. Among groups of these animals maintained 6 weeks longer on a high-fat 2-per cent cholesterol feed, the coronary lipidosis rates rose to 61 per cent when warm and 79 per cent when cold. Some of the animals in the latter group had myocardial necrosis, and a few large infarcts with completely occluded coronary arteries were observed. The pathogenesis of some of the more severe coronary lesions was explained by the presence of small dissecting aneurysms containing plasma or whole blood. It had previously been postulated that the higher metabolic rate, indicated by larger food consumption despite less weight gain, among the cold-room rats might have been related to their greater deposition of coronary lipid.

ROGERS

Smith, E. B.: Intimal and Medial Lipids in Human Aortas. Lancet 1: 799 (Apr. 9), 1960.

Fifty-six tissue samples from 22 human aortas obtained at necropsy were analyzed to see whether intimal and medial lipids showed any identity with individual lipoprotein fractions, to determine whether chemical changes occurred in the intima and media with lesions of increasing severity, and to determine whether the data suggested a different origin for lipid in different types of lesions. Concentrations of total lipid in normal intima and media were similar, but intima

lipids contained 40 per cent cholesterol and 20 per cent phospholipid, with equal parts of sphingomyelin and lecithin, whereas medial lipids had less cholesterol, more phospholipid and a greater proportion of sphingomyelin. The proportion of free to esterified cholesterol was greater in the media. The lipid content of normal intima correlated with age after 35. There was no correlation between the severity of atherosclerosis and the lipid content of normal patches of intima or media. In areas of fatty streaking there was a three-fold increase in intimal lipid and a doubling of medial lipid. In advance lesions the concentration of lipid fell, possibly from leaching out of lipid components. When the composition of the aortic lipids was compared to that of whole plasma, a close resemblance was found between the lipids in Sf 0-12 lipoprotein and in normal intima.

KURLAND

Stamler, J., Pick, R., and Katz, L. N.: Effect of Insulin in the Induction and Regression of Atherosclerosis in the Chick. Circulation Research 8: 572 (May), 1960.

The pathogenesis and the cause of the increased incidence of atherosclerosis in diabetic patients remain obscure. Experiments were undertaken to determine the effects of exogenous insulin on coronary and aortic atherogenesis in intact chicks. In control birds transferred from an atherogenic diet to plain mash for a terminal 2-week period, significant regression of coronary atherosclerosis occurred, whereas the aortic lesions showed little change. No such regression was observed in birds that were given insulin and the mash diet during this period. This was true despite a decline in values of plasma lipids in both the control and insulin-treated birds. The failure of atherosclerotic lesions to regress in animals given insulin was not related to underfeeding. Administration of insulin during the induction of atherosclerosis had no effect on the development of the lesions.

SCHIRGER

Reinis, Z., Zoulek, D., Mestan, J., Konrad, J. and Hrabane, J.: Nutrition as an Epidemiological Factor in Atherosclerosis. Cor et Vasa 1: 85, 1959.

Blood fats were determined in the same laboratory in 242 clinically healthy, industrial and agricultural workers, from different rural areas of Czechoslovakia, and 108 corresponding persons from Korea and Vietnam. Cholesterol, total lipids, and phospholipids were considerably lower in the Far East than in Czechoslovakia, at all ages and in both sexes, while the percentage of alpha and beta lipoproteins was slightly lower. In 10 Korean students who had lived in Czechoslovakia for 2 years, total lipids were significantly elevated, in comparison with Korean values, while cholesterol and phospholipids were not significantly increased. The average food intake was 3000 calories in Czechoslovakia, with 32 per cent derived from fat (nearly all of animal origin) while in the Far East this intake was 2100 calories, with 5 per cent derived from fat intake (nearly all of vegetable origin). Of 614 autopsies performed in Korea in 1957, only 1 per cent showed systemic and 0.4 per cent coronary arteriosclerosis. In Czechoslovakian agricultural areas mortality due to arteriosclerosis was 1.8 per cent of 5625 hospitalized patients, while the overall mortality in Czechoslovakia was 7.7 per cent, and the rate due to coronary disease was 0.22 per cent of the entire population. This mortality rate was between Switzerland and The Netherlands, where the daily fat consumption is about 20 per cent higher. These discrepancies can be explained by more intense physical work in Czechoslovakian rural areas. In addition to nutritional factors, those of environment and especially occupation must therefore be considered in any study of the etiology of arteriosclerosis.

LEPESCHKIN

BLOOD COAGULATION AND THROMBOEMBOLISM

Andersen, M. N., Mendelow, M., and Alfano, G. A.: A Comparative Study of Heparin Neutralization and the Danger of Blood Clotting Abnormalities with Protamine and Polybrene. J. Thoracic Surg. 39: 613 (May), 1960.

This study was performed on adult mongrel dogs. Polybrene and protamine sulfate were compared in regard to heparin neutralization and neutralizing dosage levels. The anticoagulant effect of each drug in vitro was also compared at dosage levels commonly employed clinically. Twenty animals each with protamine and polybrene were studied. No significant difference between these two drugs was noted in the incidence of inhibition of coagulation. The coagulation time appeared to be slightly more prolonged with Polybrene than with protamine in several instances. Complete neutralization of the heparin with restoration of clotting time to normal occurred with each drug in doses of 75 per cent or more by weight of the original heparin doses. It appears from these experiments that the commonly used neutralizing dosages of 100 per cent to 200 per cent by weight of the heparin given are unnecessarily large. In fact it may be haz-

ardous through protamine or Polybrene inhibition of clotting. There was no superiority of either drug in the effects studied here.

LEVINSON

Chapple, R. V., and Singher, H. O.: Role of Fibrinolytic Agents in Thrombotic Diseases. J. A. M. A. **173**: 221 (May 21), 1960.

Comparison of data from hospital charts of 20 patients in a fibrinolysin-treated series and in a group of 22 patients showed that fibrinolysin in conjunction with anticoagulant therapy decreased morbidity in patients with thrombophlebitis. While this decrease in morbidity is noted, there is still need of more exact methods of diagnosis and criteria of effectiveness. The authors review theories of clot lysis with the realization that a final answer has not yet been determined.

KITCHELL

Deaton, H. L., and Anlyan, W. G.: Treatment of Thrombophlebitis with Streptokinase-Streptodornase. J.A.M.A. **172**: 1891 (Apr. 23), 1960.

The buccal administration of streptokinase-streptodornase was tried in the treatment of 52 patients who had superficial thrombophlebitis as a complication after venoclysis. Twenty-two similar cases were observed as controls for the same period. This latter group received only general treatment without specific drugs or placebo. Evaluation was done by an investigator who did not know, in most instances, whether the patient was in the treated or the control group. Under these conditions no difference between the two groups was found and no evidence of therapeutic or prophylatic action was noted.

KITCHELL

Duthie, H. L., and Smith, G.: Failure of Phenindione to Prevent Intravascular Clotting. Scot. med. J. **5**: 265 (June), 1960.

Three cases are presented in whom progression of thrombosis (one arterial and two venous) occurred while patients were well anticoagulated with phenindione. Moreover, two patients bled spontaneously while thrombosis was taking place. The authors allude to the distinction between the antithrombotic and the anticoagulant effects of this group of drugs.

SHEPS

Fearnley, G. R., Ferguson, J., Chakrabarti, R., and Vincent, C. T.: Effect of Beer on Fibrinolytic Activity. Lancet **1**: 184 (Jan. 23), 1960.

The effect of beer and other alcoholic drinks on blood fibrinolytic activity was investigated. Initial studies revealed that the lysis-times of two subjects were greatly prolonged on days in which beer, cider, and white wine were taken, but not after gin, whiskey, or absolute alcohol. Reduction of fibrinolytic activity which reached 300 per cent was maximal after two hours. These findings were confirmed in 10 of 14 other subjects. Whiskey containing the same amount of alcohol had no effect on fibrinolysis. Absolute alcohol yielded inconclusive results. The evidence suggests that some fermentation product other than ethyl alcohol is responsible for the change. No change in the social amenities was recommended.

KURLAND

Hougie, C., and Ayers, F.: Lipaemia and Fibrinolytic Potentiality. Lancet **1**: 186 (Jan. 23), 1960.

Platelet-rich and platelet-poor plasma was obtained from each of 10 normal subjects, and the lysis rates were compared. After 1 hour, there was more lysis in the platelet-poor plasma. The addition of washed platelets inhibited the fibrinolytic activity of platelet-poor plasma. The addition of cephalin to platelet-poor plasma had no significant effect on lysis. No difference in lysis could be shown after fatty and non-fatty meals. There was a normal diurnal fluctuation in lysis rate and a significant fluctuation from day to day. There was no significant correlation between cholesterol level and fibrinolytic potentiality.

KURLAND

Lewis, J. H.: Effects of a High Fat Meal on Coagulation in Hemophilia. J. Lab. & Clin. Med. **55**: 245 (Feb.), 1960.

A possible correlation between ingestion of high-fat meals and accelerated coagulation of blood was studied. A high-fat breakfast was fed to 10 patients suffering from hemophilia A (AHF deficiency) and six subjects with hemophilia B (PTC deficiency, Christmas disease). In addition, 7 normal subjects were used as controls. Blood samples were taken after 12- to 15-hour fasting states and 3 hours following the high-fat meal. Clotting times, prothrombin times, and consumption activity, platelet counts, and proconvertin and proaccelerin activity, as well as AHF and PTC activity, were performed on all specimens. Results revealed no differences in clot-accelerating activity between normal and hemophilic blood. In vitro studies, in which fat was added, also revealed no differences, except for an acceleration of the Russell viper-venom time in normal subjects.

MAXWELL

Mancsel, J., and Dreyfuss, F.: Effect of Prednisone on Blood Coagulation Time in Patients on Dicumarol Therapy. J. Lab. & Clin. Med. **56**: 14 (July), 1960.

Whole blood coagulation time was significantly accelerated by the oral administration of 10 mg. of prednisone in 24 patients who had previously received Dicumarol for several days. The mean silicone coagulation time in these patients was 28.10 ± 2.59 minutes before the administration of prednisone. Two hours after administration it was 23.90 ± 2.23 minutes, and 4 hours after administration, it was 22.00 ± 1.85 minutes. In control patients without anticoagulation treatment, the mean silicone coagulation time had been previously determined as 16.22 ± 0.542 minutes. No conclusions could be drawn as to which clotting factors were influenced by the administration of prednisone, but the authors assumed that prednisone mobilized or replaced convertin activity, as ACTH and cortisone have been observed to do.

MAXWELL

Messinger, W. J., and Weiner, J.: An Evaluation of Some Clotting Tests in Patients Receiving Coumarin Drugs. Arch. Int. Med. **105**: 727 (May), 1960.

A special coagulation laboratory was set up at the North Shore Hospital, Manhassett, New York, to evaluate the criticisms of the one-stage prothrombin test as a guide to anticoagulant therapy. Contrary to popular thinking by some laboratory workers, the one-stage prothrombin test can be accurately reproduced. Blood specimens from three normal subjects and five patients on anticoagulant therapy were divided into 40 tubes and code-labeled. The results were almost identical in every instance. Studies were made to determine the value of citrated plasma versus oxalated plasma stored at the same temperatures for the same periods of time. Citrated plasma was less labile and when mixed with the calcium thromboplastin reagent, less clouding occurred than when using oxalated plasma. This allowed for sharper observaton of the coagulation end point. Storage temperatures were not critical factors as long as the tests were done within 6 hours after collection of the blood specimens. Further study indicated the value of review of laboratory procedures when incidence of either bleeding or thromboembolism was high. In all such instances the technic was most important and small deviations in the method produced differences in test results between the general laboratories and the special laboratory. In each instance under supervision the general laboratory technician was able to reproduce the same results as the special laboratory technician. The authors feel that the one-stage prothrombin test is still the best provided that it is accurately performed and properly interpreted.

KRAUSE

Newcomb, T. F., Robin, E. D., Travis, D. M., and Julian, D. G.: Blood Coagulation During Sleep. J. Lab. & Clin. Med. **56**: 25 (July), 1960.

Normal individuals without known involvement of the hematopoietic system were the subjects of this study. Blood samples were obtained by the use of an indwelling polyethylene catheter in an arm vein. The parameters of blood clotting, which were measured during waking, sound sleep, and intermediate states, at hourly intervals throughout the night were: Quick prothrombin, prothrombin-proconvertin (Owren), proaccelerin, Russell's viper-venom time, partial thromboplastin time, fibrinogen, platelet count, euglobulin, lysis time, and thromboplastin generation test. No significant differences in blood coagulability were found between the normal person in the waking state and the normal person sleeping without sedative drugs.

MAXWELL

Nunez Ramos, C., Torres, P., Ramallo, M., and Vidal, J.: Phlebothrombosis: Clinical Study and Treatment. Canad. M.A.J. **83**: 16 (July 2), 1960.

Observations over a 4-year period of 52 patients with phlebothrombosis were described. Ages ranged from 18 to 60 years, and 83 per cent were women. The duration of the disorder varied from 2 weeks to 7 months in all except one case of 18 months' standing. In 48 instances the process was unilateral, involving the left leg in 21, the left thigh in 14, the right leg in 12, and the right thigh in eight. The diagnosis was based on the presence of local discomfort, edema, and the results of tests, including limb measurements, thermometry, Homans', Buerger's, and Collens-Willensky's tests, the calf pressure test, and the femoro-digital arterial circulatory time. Treatment consisted of prothrombin depressants, phenylbutazone, 600 mg. daily, and chlorothiazide 1 to 2 tablets daily—all for a minimum of 3 weeks. Elastic bandages during the day were ordered for a 6-month period, dorsolumbar heat was prescribed when there was evidence of arterial spasm, and all patients were ambulatory. The results were excellent and included a return to normal of limb measurements in an average of 3.2 day, of Homans' test in 5.7 days, of calf

pressure test in 11.5 days, of leukocyte count in 16.3 days, and of erythrocyte sedimentation rate in 18.5 days. The incidence of embolization was not mentioned. The importance of considering the possible presence of phlebothrombosis in patients having dysmenorrhea with edema or atypical signs of appendicitis was noted.

ROGERS

Nilsson, I. M., Sjoerdsma, A., and Waldenstrom, J.: Antifibrinolytic Activity and Metabolism of ε-Aminocaproic Acid in Man. Lancet 1: 1322 (June 18), 1960.

ε-aminoe-n-caproic acid (ACA) is a plasmin inhibitor in vitro which is useful in inhibiting proteolytic enzymes in vivo. The effect of ACA on the blood fibrinolytic system was studied in two patients who had pronounced fibrinolysis and one with increased plasminogen activators. The rate of its disappearance from plasma and the amount excreted in the urine were also measured in four subjects. ACA temporarily abolished pathologic fibrinolysis in two patients, and one showed clinical evidence of a therapeutic response during maintenance therapy. In the third, a great increase in plasminogen activator gave clear evidence of the inhibitory action of ACA on plasminogen activator in vivo. The drug was effective by the intravenous route or was efficiently absorbed after oral administration, but large doses were necessary for an effective level, and rapid urinary excretion necessitated therapy every 4 to 6 hours. Postmortem examination in three patients showed no apparent toxic effects of the drug, but renal function should be watched closely when ACA is given in large dosage.

KURLAND

Poller, L.: The Possible Relationship between the Antiheparin Activity of Serum and Thrombosis. J. Clin. Path. 13: 226 (May), 1960.

Storage of serum reduces the effect of heparin on the clotting time of normal serum and on serum from patients with Christmas disease (factor IX deficiency), and also in serum with factor VII deficiency and serum from patients treated with phenindione. The antiheparin agent is distinct from factor VII and Christmas factor since it did not appear to be appreciably reduced by treatment with phenindione. It resembles these two factors, however, by being in the serum in excessive amounts and by being observed and subsequently eluted from alumina. It was suggested that heparin "resistance" might have a part in predisposing to thrombosis, but the possibility also remained that it might be a secondary effect that was due to the release of serum products from the thrombus into the circulation. The possibility was also suggested that antiheparin activity of the serum may have a part in the production of intravascular clotting, perhaps by furthering a pre-existent clotting tendency. It was suggested that the coagulant factor of serum demonstrated by Wessler may be related to the antiheparin agent of the serum demonstrated by the author. The importance of this in the pathogenesis of thrombosis is uncertain as yet, but it may play a role in bringing about increased coagulability associated with recent thrombus formation.

SCHIRGER

Shoshkes, M., and Tami, M.: Dihydrovitamin K_1 Biphosphate in Bishydroxycoumarin Induced Hypoprothrombinemia. J. Lab. & Clin. Med. 56: 21 (July), 1960.

Effects of the oral administration of a new water-soluble salt of vitamin K_1 (dihydrovitamin K_1 biphosphate) are described when it was tested clinically as an antidote in 41 adult hospitalized patients. These patients had been under Dicumarol therapy, usually for weeks, until levels of hypoprothrombinemia had been stabilized. This water-soluble vitamin was found to be ineffective as an antidote in oral doses ranging from 5 to 50 mg. over a 24-hour period. It was also ineffective in doses smaller than 50 mg. when given intravenously or subcutaneously, as well as in intramuscular doses of 50 mg. Since initial favorable reports on the water-soluble drug were limited to experiments on dogs, the authors conclude that it is not warranted to replace the oil-soluble vitamin K_1 now in use, except for specific investigative purposes.

MAXWELL

Toohey, M., and Cook, I.J.Y.: Automatic Clotting-timer for Control of Anti-coagulant Therapy. Brit. M. J. 1: 1620, (May 28), 1960.

The authors have devised an automatic time-recording apparatus that can be used for measuring the clotting time of plasma such as the recalcified plasma clotting time, Quick's one-stage technic, Owren's original "P and P" method, and the more recent thrombotest using plasma. This apparatus has a time recording switch, aperture, galvanometer sensitivity control, and a clock. All these tests are carried out in the usual manner except for glass tubes of special size to fit the apparatus. It is also important to use sodium citrate instead of oxalate in collecting blood samples. As soon as the calcium is added the time recorder is started. The tube is inverted to mix the contents and then inserted in the aperture. By turning the galvanometer control, the gal-

vanometer needle is adjusted midway between the two marks on the galvanometer scale. Several seconds are allowed to permit any drift of the needle. Once the needle is steady for a few seconds, the time-recording switch is moved in the opposite direction than previously and this brings into action an automatic cut-out switch. When clotting starts, a turbidity develops in the plasma. The turbidity causes the galvanometer needle to shift, and this causes the cut-out switch to operate and stops the time-recording apparatus. The test can then be read. Once the automatic timer is activated no further attention is needed. The operator may leave the laboratory and return at any time and read the results of the test. It also allows duplicate tests to be carried out at the same time. This apparatus not only saves time but allows for standardization in reading results and does away with discrepancies in interpreting time.

KRAUSE

Verstraete, M., Vermylen, C., and Vandenbroucke, J.: Measurement of Overall Coagulability during Coumarin Treatment with Reference to the Quick Test. Acta Med. Scandinav. **167**: 127, 1960.

Coumarin type anticoagulants decrease the activity of factor VII, prothrombin, Stuart-Prower factor, and factor IX (Christmas factor). The commonly used one-stage prothrombin time of Quick does not reflect changes in the latter factor. Moreover, changes in the concentration of factor VII give erratic results, depending on the type of tissue thromboplastin used in the Quick test. To assess which of the various tests of coagulability more accurately reflected the effect of the Coumarin drugs, the following tests were carried out and compared with the one-stage prothrombin time: bleeding time, clotting time, recalcification time, heparin tolerance test, sodium chloride tolerance test, thromboplastin generation test, modified thromboplastin generation test, and the P. and P. test of Owren. Thromboelastographic procedures were also discussed. The authors discuss these tests in detail and conclude that the P. and P. method of Owren is the most reliable guide to long-term anticoagulant therapy. This test reflects the changes in the concentration of factor VII at the beginning of therapy and later, when the activity of this factor is low (decreased by coumarin effect and by dilution in the technic), the test becomes an expression of the concentration of factor IX (also reduced by the coumarin drugs). No comment is made regarding the clinical incidence of hemorrhage in relation to these various procedures.

SHEPS

CONGENITAL ANOMALIES

Alzamoro-Castro, V., Battilana, G., Abugattas, R., and Sialer, S.: Patent Ductus Arteriosus and High Altitudes. Am. J. Cardiol. **5**: 761 (June), 1960.

Among 27,000 case histories in a cardiology department in Lima, Peru, 110 instances of patent ductus arteriosus and 32 of coaretation of the aorta were found. It was thought that the patients seen in this medical center were fairly representative of the whole population of Peru where, above 4,000 meters altitude, 3 per cent of the people were born and 2 per cent lived. Twenty per cent of the patent ductus patients were born at levels higher than 4,000 meters, whereas the remainder of this group and the whole of the coaretation group were born at altitudes paralleling that of the general population. Considering the experimental evidence that oxygen is an important factor involved in closing the ductus arteriosus, the authors suspected that the lowered atmospheric oxygen tension at high altitudes might have been responsible for this seven-fold increase in the incidence of ductus patency.

ROGERS

Bentivoglio, L. G., Sagarminaga, J., Uricchio, J., and Goldberg, H.: Congenital Bicuspid Aortic Valves. Brit. Heart J. **22**: 321 (June), 1960.

The authors reviewed the clinical, radiographic, electrocardiographic, and hemodynamic data of six proved cases of congenital aortic stenosis, five of which were associated with varying degrees of commissural fusion. One patient with a normal roentgenogram and electrocardiogram showed no systolic gradient across the aortic valve and no evidence of commissural fusion. The other patients with varying degrees of commissural fusion showed slight to moderate systolic gradients not exceeding 43 mm. Hg with left axis deviation or left ventricular hypertrophy by electrocardiogram. One patient had an aneurysm of the sinus of Valsalva of the right coronary cusp, which was thought to be secondary to the jet of blood on the aortic wall. The one patient without evidence of a systolic gradient across the aortic valve had evidence of a systolic murmur at the aortic area transmitted to the neck, and dilatation of the aorta. None of the patients had decreased intensity of the aortic second sound in contrast to patients with acquired aortic stenosis. The authors believe that congenital bicuspid aortic stenosis plays a more important role in the group with congenital aortic stenosis than has been recognized.

KALMANSOHN

Berg, J. M., Crome, L., and France, N. E.: Congenital Cardiac Malformations in Mongolism. Brit. Heart J. **22**: 331 (June), 1960.

This report was based on the necropsy data of five hospitals of all the patients with mongolism. Seventy-nine patients with cardiac malformations were compared with 300 control patients. It was emphasized that the varying incidence of cardiac malformations in different series of patients with mongolism is due to the different age ranges or methods and criteria upon which the diagnosis of congenital heart disease is made. On a qualitative basis, the concept of a "mongol" heart did not appear to be justified as the variety of cardiac malformation was as wide in the mongol group as in the control group. However, persistent ostium primum and varieties thereof as well as atrial septal defects of the ostium secundum type were more frequently noted in the patients with mongolism. Fallot's tetralogy, Eisenmenger's complex, persistent truncus arteriosus, left superior vena cava, coaretation of the aorta of the adult type, anomalies of the aortic and pulmonic valves, and fibroelastosis were less frequently noted in the cases of mongolism. Ventricular septal defect, patent ductus arteriosus, and idiopathic cardiac hypertrophy were noted equally in both groups.

KALMANSOHN

Espino Vela, J., Garcia Madrigal, R., Perez Martin, R., and Gonzalez, C.: Congenital Cardiopathies and Pregnancy. Arch. Inst. cardiol. México **30**: 117 (Mar.-Apr.), 1960.

The tolerance of the heart to the malformation was evaluated in 117 women with congenital heart disease prior to and during pregnancy. The following conclusions were reached. In heart disease characterized by an arteriovenous shunt, perhaps the most important factor responsible for the overloading of the heart is volumetric overloading, represented by the increased flow through the lungs. Often, if this factor is complicated by the increased mechanical work represented by elevation of the pressure within the cardiac chambers, the summation of adverse effects will probably lead to heart failure. In venous-arterial shunts tolerance of the heart to pregnancy appeared related to the degree of anoxemia pertaining to the malformation. In congenital heart disease with an obstacle to the ejection of one of the ventricles, the most important factor in prognosis was the hypertension of the overloaded ventricle. In aortic coaretation the dangers appeared to derive principally from the effects on the vessels (rupture of the aorta, dissecting aneurysm, cerebral aneurysm), rather than to a direct effect on the myocardium. There is no formal contraindication to surgical correction of the malformation during the first trimester of pregnancy, nor does the procedure seem to entail any danger to the child. It may be a perfectly warranted indication if the pregnancy is poorly tolerated. Cesarean operations have a very limited indication in these women and should perhaps be limited to the treatment of gyneco-obstetric problems. The tolerance of the patient to her malformation prior to pregnancy is a useful guide, as a rule, in the prognosis of the tolerance to the pregnancy.

BRACHFELD

Fabio Lion, M., and Pinenta de Campos, E.: Congenital Complete Auriculo-ventricular Block in a Patient with Endocardial Fibroelastosis and Persistence of Ductus Arteriosus. Diagnosis in Utero. Arch. Inst. cardiol. México **30**: 187 (Mar.-Apr.), 1960.

The case of a rare association of several congenital heart malformations (complete A-V block, endocardial fibroelastosis, and a patent ductus arteriosus) is reported. The complete atrioventricular block was suspected during pregnancy due to the low heart rate of the fetus. It was confirmed on the first day of life with the electrocardiogram. The heart rate was extremely low, with a ventricular rate of 25 beats per minute. Endocardial fibroelastosis was confirmed by macroscopic and microscopic examination. Both ventricles and the left atrium were involved. It was more marked over the left ventricle. The heart was four times the normal size; its weight was increased. The myocardium of the left ventricle was twice as thick as normal and its endocardium 10 times as thick as normal. The ductus arteriosus was patent. The child, born prematurely, died after 36 days of extreme dehydration.

BRACHFELD

Gillman, H., and Lohr, B.: Correlative Study of Electrocardiograms and Operative Findings in Ventricular Septal Defects. Cardiologia **36**: 232, 1960.

In 20 of 33 patients with isolated ventricular septal defect the total area of the defect was less than 1 cm.^{2} Electrocardiograms without definite abnormalities were found in only seven patients. Disturbances of conduction resulting in an enlarged area of QRS vector loops (with corresponding changes in the electrocardiogram) were only to a limited extent related to the size of the defect. The functional significance of the defects depended on their size and localization.

BRACHFELD

Glass, I. H., Mustard, W. T., and Keither, J. D.: Coarctation of the Aorta in Infants. Pediatrics **26**: 109 (July), 1960.

The authors review 108 cases of aortic coarctation diagnosed in the first year of life during the period of 1947 to 1959. Associated major cardiac anomalies included patent ductus arteriosus (65 per cent), intraventricular septal defect (33 per cent), transposition of the great vessels (10 per cent), and interatrial septal defects (6 per cent). Infantile (preductal) coarctation accounted for 90 per cent of the infant fatalities. Operative mortality in the entire first year of life was 41 per cent while after 1 year of life it was only 29 per cent. Death occurred in 87 per cent of patients with cardiac decompensation during the neonatal period, whereas it occurred in only 50 per cent of the nonsurgical patients during the first year of life. The authors emphasized that aortography should be performed on all diagnostic problems, that surgery should be performed on symptomatic babies less than 1 month old unless they show a dramatic response to digitalis therapy within 12 hours, and that those babies that respond to digitalis should continue to be medicated until the optimum age for surgery is reached.

KARPMAN

Herbst, M., Bock, K., Hartleb, O., and Fiehring, H.: Supravalvular Aortic Stenosis with Aortic Hypoplasia Fortsch. Röntgenstr. **92**: 533, (May), 1960.

The first patient, a 6-year-old girl, showed aortic configuration of the heart with a narrow vascular shadow, a typical diamond-shaped systolic murmur transmitted to the neck, and right axis deviation with deep S waves in V_1 to V_7 in the electrocardiogram. Direct left ventricular puncture with dye injection showed a systolic pressure gradient of 60 mm. Hg between left ventricle and femoral artery and an abrupt marked narrowing of the aorta 1 cm. above the valves, extending to the entire thoracic and abdominal aorta. The second patient, a 25-year-old man, showed a similar cardiac configuration but only a soft systolic murmur, and dominant S waves in leads I to III and V_2 to V_6 with inverted T waves in leads I and II. Right heart catheterization and angiocardiography showed a slit-like narrowing of the right ventricle with a systolic gradient of 46 mm Hg. Direct puncture of the left ventricle with dye injection showed an abrupt narrowing of the aorta above the coronary arteries, extending to the entire thoracic aorta, and marked hypertrophy of the left ventricular wall. The right ventricular narrowing in this case was accordingly part of the Bernheim syndrome. Since aortic hypoplasia cannot at present be successfully treated by surgery, its differentiation from localized aortic stenosis is important; this can be suggested by the narrow vascular shadow and electrocardiographic findings, but proved only by means of direct left ventricular injection of contrast medium. A congenital origin of this malformation is certain.

LEPESCHKIN

VALVULAR HEART DISEASE

Mustard, W. T., Rowe, R. D., and Firor, W. B., Jr: Pulmonic Stenosis in the First Year of Life. Surgery **47**: 678 (Apr.), 1960.

The results of surgery in 13 infants with congenital pulmonic stenosis is reported. Three infants were operated on using the transventricular operation. The remainder were performed by direct vision, transarterial, pulmonary valvulotomy by means of hypothermia with inflow occlusion. The patients were followed for periods ranging from 2 weeks to 6 years. Of the 11 cyanotic infants who survived operation, 9 have had complete or at least significant reduction in the intensity of cyanosis. One child has slight residual cyanosis at rest which becomes marked on crying and another had early improvement which gradually deteriorated and required re-operation 6 years later. The changes in the murmurs postoperatively were not dramatic—the intensity remained the same or was slightly decreased. In 1 child it disappeared altogether. Over the age of 5 weeks, right ventricular hypertrophy was invariably found on electrocardiography. The majority of satisfactory surgical procedures were followed by a reduction in voltage of the R wave in V_1 and other signs of lessening of right ventricular hypertrophy for at least 6 months. There were 2 deaths. One of these was in an infant operated on at the age of 9 months. She died at operation following completion of a transventricular valvulotomy. Necropsy revealed valvular and infundibular stenosis to be present, and in addition it was noted that the knife had missed the valve completely and had cut into the mediastinum instead. The other fatality was of a male infant who underwent transventricular valvulotomy at the age of 3 months. There was only moderate clinical improvement but because of progressive unrelated neurologic disease, further surgery was not performed. He later succumbed to the latter conditions. The clinical picture is described and the use of selective angiocardiography is emphasized in differentiating pulmonic atresia or pulmonic stenosis with normal aortic root. Angiography, moreover, permitted determination of right ventricular cham-

ber size which determined the success or failure of treated cases.

SHEPS

Selzer, A.: Effects of Atrial Fibrillation upon the Circulation in Patients with Mitral Stenosis. Am. Heart J. 59: 518 (Apr.), 1960.

In a series of 67 patients with mitral stenosis it was shown that the occurrence of more advanced circulatory abnormalities in patients with atrial fibrillation was related primarily to the more common occurrence of this rhythm in the advanced cases of mitral stenosis. The effect of atrial fibrillation on the circulatory dynamics of patients with mitral stenosis was evaluated by hemodynamic measurements in 3 patients studied once while in sinus rhythm and again when in atrial fibrillation and in 15 pairs of patients matched in all respects except for cardiac rhythm. There was no significant difference in the level of pulmonary arterial pressures and the pulmonary vascular resistance between those patients in sinus rhythm and those in atrial fibrillation. The cardiac output, both at rest and during exercise, however, was found to be consistently higher in patients with sinus rhythm than in those with atrial fibrillation. The left atrial pressure also was significantly lower in the fibrillators, but this was considered to be a secondary response to lowered cardiac output. The reduction of cardiac output which develops when atrial fibrillation, even under optimal digitalis control, complicates mitral stenosis is postulated as a factor possibly accentuating clinical disability in some patients.

SAGALL

VASCULAR DISEASE

Brown, D. B., Graham, A. G., and Toomey, W. F.: Recurrence of Varicosity following "High Ligation." Scottish M. J. 5: 88 (Feb.), 1960.

The recurrence of varicosities following "high ligation" of the long saphenous system among 97 patients was reviewed. Eighteen of these patients had bilateral recurrences. The average time interval that elapsed before recurrence became evident was 7 years. The groin was explored because of incompetence at the saphenofemoral junction in 98 limbs. The cause of the reflux was found to be an inadequate operation leaving 1 or more tributaries intact. The deep external pudendal branch joining the medial aspect of the long saphenous vein was the channel most liable to be overlooked. In 37 legs, incompetent communicating veins were found; these were the sole cause of recurrence in 10 of these limbs. Incompetent communicating veins were usually found in the middle and lower third of the thigh. These incompetent communicating veins must be dealt with at the initial procedure to prevent recurrence. In 11 limbs there were venous ulcers. These were all associated with saphenofemoral incompetence. In addition there was an incompetent communicating vein in the lower third of the thigh in 2 limbs. In 4 of these limbs ulceration was present prior to the initial "high ligation." These broke down again from 1 to 6 years following the initial ligation. The short saphenous system played a minor role in this series.

SHEPS

Crane, C.: Venous Interruption for Septic Thrombophlebitis. New England J. Med. 262: 947 (May 12), 1960.

The literature concerning the surgical treatment of septic thrombophlebitis is reviewed and 3 cases of septic thrombophlebitis treated by proximal venous interruption are presented. It is pointed out that septic thrombophlebitis often feeds a septicemia and that inlying intravenous catheters often are the source of such sepsis, especially in already septic debilitated patients. The author summarized intravenous catheter management as follows: an arm vein should always be used if possible; the catheter should be removed in 48 hours; the tip of the catheter should be cultured; and the local use of heparin should be considered in each case.

SAGALL

Gillespie, J. A.: Late Effects of Lumbar Sympathectomy. Lancet. 1: 891 (Apr. 23), 1960.

This study reports measurement of blood flow by venous occlusion plethysmography in the 61 available surviving non-amputated limbs of a consecutive series of 100 patients sympathectomized between 1 and 7 years previously for obliterative vascular disease. In 38 of 46 patients who had had a unilateral sympathectomy, the resting blood flow in the sympathectomized foot exceeded that in the non-sympathectomized foot, the average flow being nearly twice as great. This figure probably underestimates the effect of the procedure. There was no evidence that the effect of sympathectomy on blood flow in the foot diminished with the passage of time between 1 and 7 years after operation. Recovery of sympathetic vasomotor activity was measured by the body heating test. In only 11 per cent of limbs was there evidence of late partial recovery of sympathetic control. Even where there was some recovery of sympathetic activity, the increase in flow on heating seldom exceeded 50 per cent, and the resting flow was always higher in the operated limb. It is suggested that lumbar

sympathectomy is a good operation for promoting the healing of existing ischemic skin lesions and the prevention of further ones.

KURLAND

Groch, S. N., Jurwitz, L. J., Wright, I. S., and McDowell, F: Bedside Diagnosis of Carotid Artery Occlusive Disease. New England J. Med. **262**: 705 (Apr. 7), 1960.

Study of the records of 57 patients with occlusive disease of the carotid artery (established either by angiography or by surgical exploration) revealed certain features of bedside diagnostic significance. Important clues in the history were repeated transient ischemic attacks, particularly ipsilateral visual disturbance with contralateral motor or sensory deficit, and somnolence. Physical findings of help in diagnosis were Horner's syndrome, cervical and ocular bruits and absent carotid artery pulsations in the pharynx. The most reliable diagnostic measure was ophthalmodynamometry, for in 77 per cent of the patients in this series a reduced retinal artery pressure was found on the side of the proved occlusion. By the use of such readily performed maneuvers as ophthalmodynamometry and palpation of the internal carotid artery in the posterior pharynx in every patient who has experienced a stroke, it should be possible to uncover patients with occlusive carotid artery disease who would otherwise be diagnosed as having had thrombosis of the middle cerebral artery.

SAGALL

Mavor, G. E., Davidson, L. D., and Clark, C. G.: The Ruptured Abdominal Aortic Aneurysm and Its Treatment. Brit. J. Surg. **47**: 292 (Nov.), 1960.

It is justifiable to resect the symptomless abdominal aortic aneurysm before rupture and to reconstruct the aorta with a homograft or plastic prosthesis, but since many cases are not seen until after rupture has occurred, it becomes imperative to make the diagnosis early and to operate immediately. Four patients are described. One lived 3 months. Another, in whom the duration of rupture was only 10 hours and in whom surgery was performed within 1½ hours of collapse, recovered completely. Various points in anesthetic and operative management, including the amounts of blood generally required at each stage of the operation, are discussed. The tendency to overtransfuse after application of the aortic clamp is mentioned, as well as the advisability of reserving at least 2 pints of blood for use on release of the aortic clamps, if hemorrhage is excessive. The advantages of a homograft over a prosthesis are described. It is important to use heparin locally in all anastomoses and to inject it distally in a considerable volume of saline into the femoral arteries.

MAXWELL

Roedling, H. A., Roth, G. M., Schirger, A., and Gifford, R. W., Jr.: Effect of Nylidrin Hydrochloride on the Skin and Muscle Temperatures of Patients with Occlusive Arterial Disease of the Lower Extremities. Angiology **2**: 130 (Apr.), 1960.

Ten patients with intermittent claudication received 5 mg. of nylidrin hydrochloride intramuscularly, and 3 subsequently received this dose intraarterially. During the hour thereafter no significant change was observed in the temperature of the skin of the fingers, toes, and calf or in that of the gastrocnemius muscle, nor did the tolerance for walking change. It was concluded that vasodilatation did not occur in these areas, and the question was raised whether any drug could have produced vasodilatation of the leg arteries in these patients.

ROGERS

REVIEWS IN CARDIOVASCULAR DISEASE

Grayzel, J.: Gallop rhythm of the heart. I. Atrial gallop ventricular gallop and systolic sounds. Am. J. Med. **28**: 578 (Apr.), 1960.

Miasnikov, A. L.: Diagnostic and pathogenic borderlines between hypertensive disease and atherosclerosis. Am. J. Cardiol. **5**: 692 (May), 1960.

Bjurulf, P.: Atherosclerosis and body-build. With special reference to size and number of subcutaneous fat cells. Acta med. scandinav., Suppl., 349, accompanies vol. 166, 1960.

Schoenmackers, J.: Ueber bronchialvenen und ihre Stellung Zwischen Grossem und kleinen Kreislauf. Arch. Kreislaufforsch. **32**: 1 (Feb.), 1960.

Price, H. L.: General anesthesia and circulatory homeostasis. Physiol. Rev. **40**: 187 (Apr.), 1960.

Tobian, L.: Interrelationship of electrolytes, juxtaglomerular cells and hypertension. Physiol. Rev. **40**: 280 (Apr.), 1960.

Hale, A. R., and Burch, G. E.: The arteriovenous anastomoses and blood vessels of the human finger. Medicine **39**: 191 (May), 1960.

Phillips, J. H., and Burch, G. E.: A review of cardiovascular diseases in the white and Negro races. Medicine **39**: 241 (May), 1960.

NEWS FROM THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, New York
Telephone Gramercy 7-9170

Applications for Research Support Are Invited by Heart Association

Applications from research investigators for support of studies to be conducted during the fiscal year beginning July 1, 1962, are now being accepted by the Association.

The deadline for submitting applications for Research Fellowships and Established Investigatorships is September 15, 1961.

This also is the final date on which the Association will accept applications for Research Fellowships. In future, state and local Heart Associations will assume responsibility for supporting individuals in this category. Those applying in September may request either one or two-year appointments.

Applications in the Grants-in-Aid category must be received by November 1, 1961.

Awards will be made as follows:

Established Investigatorships: Usually awarded for five years, subject to annual review, in amounts ranging from $7500-$9900 yearly plus dependency allowances, to scientists of proven ability who have developed in their research careers to the point where they are independent investigators. Additionally, a grant of $1000 is made to the investigator's institution for the support of his research program. Applicants for Established Investigatorships may also apply for a grant-in-aid to support their research.

Advanced Research Fellowships: Awarded for one or two-year periods to post-doctoral applicants with some research training and experience but who are not clearly qualified to conduct their own independent research. Stipends range from $5500-$6000 annually, plus dependency allowance. During the second year of tenure, they are permitted to spend up to 25 per cent of the time in professional and scientific activities not strictly of a research nature, provided that these will contribute to their professional development and do not involve services for a fee. An additional grant of $500 is made to the investigator's department.

Research Fellowships: Awarded on a limited basis to provide training under experienced guidance for young scientists with doctoral degrees. Annual stipends range from $4500 to $7000.

Grants-in-Aid: Made to experienced investigators to help underwrite the costs of specified projects, such as equipment, technical assistance and supplies.

A limited number of investigators of unusual capacity and widely recognized accomplishment are appointed by the Association as Career Investigators to assure them of financial support throughout their productive lives. These are selected by the Association's Research Committee and *not by application.*

Further information and application forms for research awards may be obtained from the Assistant Medical Director for Research, American Heart Association, 44 East 23rd Street, New York 10, New York.

New Career Investigator Named To Receive Lifetime Support

The Association has named Earl H. Wood, M.D., Ph.D., Professor of Physiology at the Mayo Foundation, as a Career Investigator effective July 1, 1961. His appointment is the 10th in this category originated by the Association 10 years ago to provide support throughout their professional lives to scientists of outstanding ability and achievement.

Dr. Wood, who is also Consultant in Physiology to the Mayo Clinic, is well known for his many contributions to dye dilution techniques. He and his associates are identified es-

pecially with the introduction of new dyes for use in conjunction with the oximeter.

His laboratory of human physiology at Mayo Clinic is considered one of the most completely instrumented and technically advanced of its kind in the world. It has also been the site of studies with the human centrifuge to simulate acceleration and high gravity conditions, continuing an interest dating back to World War II. During the war Dr. Wood and his associates carried out studies on the physiology of fighter pilot "blackout" and helped develop an antigravity suit to combat it.

Born in Minnesota, Dr. Wood holds a Bachelor of Arts degree from MacAlester College in St. Paul. He received his Master of Science, Medical and Ph.D. degrees from the University of Minnesota. He has been at the Mayo Foundation since 1942 and has also held academic or research posts at Harvard Medical School and the University of Pennsylvania. In 1946 he was a scientific consultant to the U. S. Air Force at the Aeromedical Center in Heidelberg, Germany.

6 Programs on Clinical Cardiology Included in AHA Scientific Sessions

Six sessions on clinical cardiology designed to be of particular interest to the practicing physician will be included in the Association's 34th annual Scientific Sessions at Bal Harbour, Miami Beach, Florida. A panel or symposium with related investigative work in the clinical field will be presented at each clinical session.

Simultaneous scientific sessions will be held throughout the three-day program from Friday, October 20 through Sunday, October 22, in the Americana Hotel.

A tentative outline of the program follows:

Friday October 20: The sessions on clinical cardiology include an opening address by Oglesby Paul, M.D., AHA President; the Conner Memorial Lecture, by Dr. Clark H. Millikan, Professor of Neurology, Mayo Clinic; symposia on "Contribution of Phonocardiography to Auscultation," and on "Coronary Arteriography"; and a lecture on "Biplane Angiography" by Dr. Herbert L. Abrams, Assistant Professor of Radiology, Stanford Medical Center. Concurrent sessions are scheduled on arteriosclerosis, on biophysical methods in the study of circulation, and on high blood pressure research. A nurses' program is also scheduled.

Saturday, October 21: The clinical sessions will include a panel on "Ventricular Arrhythmias"; a lecture on "Closed Chest Cardiac Resuscitation" by James R. Jude, M.D., Johns Hopkins Hospital; the Brown Memorial Lecture on "Physiology of the Peripheral Circulation," by Robert W. Wilkins, M.D., Professor of Medicine, Boston University School of Medicine; and a symposium on "Renal Failure." Simultaneous scientific sessions will be held on the subjects of basic science, cardiovascular surgery, and on "Compensable Heart Disease, Strain and Trauma."

Sunday, October 22: Subjects for the clinical sessions include a symposium on "The Role of Hormones in Heart Failure"; panels on "Ventricular Hypertrophy and Bundle Branch Block" and "Newer Electrocardiographic Lead Systems"; and a lecture on "ECG Clues Suggesting Myocardial Infarction" by Junior A. Abildskov, M.D., Assistant Professor of Medicine, State University of New York College of Medicine. Concurrent sessions will be held on rheumatic fever and congenital heart disease and on cardiovascular surgery. Cardiovascular films, with introductions and commentary by the author or other authority on the subject, will be shown throughout Sunday.

As in previous years, scientific and industrial exhibits will be shown.

Report Projects AHA Plans For Future Physician Education

A report on "The Physician's Continuing Education," which projects future AHA activities in professional education, has been issued by the American Heart Association.

The report, prepared by the Association's Committee on Professional Education, generally analyzes the present status of professional education and current teaching methods in

this country. It indicates that many practitioners are not reached by continuing education because programs are not made available to them, and often because training courses have not been adapted to their needs.

Various techniques for physician education and the relative advantages of each are discussed. The report emphasizes the need for research in medical education and for better methods of evaluation.

Although the report was prepared for the guidance of the Association's affiliates, other agencies and institutions interested in continuing medical education will find the manual useful.

Copies may be obtained from local Heart Associations or from the American Heart Association.

Life Insurance Fund Offers Research Fellowships and Grants

The Life Insurance Medical Research Fund is now receiving applications for two types of awards to be available July 1, 1962, as follows:

(1) *Until October 1, 1961,* for postdoctoral research fellowships. Candidates may apply for support in any field of the medical sciences. Preference is given to those who wish to work on fundamental problems, especially those related to cardiovascular function or disease. Minimum stipend $4,500, with allowances for dependents and necessary travel.

(2) *Until November 1, 1961,* for grants to institutions in aid of research on cardiovascular problems. Support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field.

Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 1030 East Lancaster Avenue, Rosemont, Pennsylvania.

Meetings Calendar

June 22-26: American College of Chest Physicians, New York. Murray Kornfeld, 112 E. Chestnut St., Chicago 11, Illinois.

June 23-25: American College of Angiology, New York. Alfred Halpern, 11 Hampton Court, Great Neck, New York.

June 24: International Cardiovascular Society, North American Chapter, New York. R. A. Deterling, Jr., 171 Harrison Ave., Boston 11, Massachusetts.

June 25: Society for Vascular Surgery, New York. George H. Yeager, 314 Medical Arts Bldg., Baltimore 1, Maryland.

June 25-30: American Medical Association, Annual Meeting, New York. F.J.L. Blasingame, 535 N. Dearborn, Chicago 10, Illinois.

July 1-4: International College of Surgeons, New England Regional Meeting, Chatham, Massachusetts. M. L. Brodny, 4646 N. Marine Dr., Chicago 40, Illinois.

July 10-24: International Conference on Medical Electronics, New York. L. E. Flory, David Sarnoff Research Center, Princeton, New Jersey.

August 7-10: National Medical Association, New York. John T. Givens, 1108 Church St., Norfolk, Virginia.

August 27-September 1: American Congress of Physical Medicine and Rehabilitation, Cleveland. Dorothea C. Augustin, 30 N. Michigan, Chicago 2, Illinois.

September 26-29: American Roentgen Ray Society, Miami Beach. C. A. Good, Mayo Clinic, Rochester, Minnesota.

October 2-6: American College of Surgeons, Chicago. W. E. Adams, 40 East Erie St., Chicago 11, Illinois.

October 3-4: Congress on Occupational Health, Denver. Council on Occupational Health, American Medical Association, 535 N. Dearborn, Chicago 10, Illinois.

October 14-20: International Congress of Neurosurgery, Washington, D. C. Bronson S. Ray, 525 E. 68th Street, New York 21, New York.

October 17-19: International Seminar on Vascular Systems, Miami Beach. John B. Liebler, Heart Association of Greater Miami, 253 S.W. 8th St., Miami 36, Florida.

October 18-20: Council on Arteriosclerosis of American Heart Association, Miami Beach. Jeremiah Stamler, Chicago Board of Health, 54 West Hubbard, Chicago 10, Illinois.

October 20-24: American Heart Association, Annual Meeting and Scientific Sessions (October 20-22), Bal Harbour, Florida. American Heart Association, 44 East 23rd St., New York 10, New York.

November 13-17: American Public Health Association, Detroit. Berwin F. Mattison, 1790 Broadway, New York 19, New York.

November 16-18: International Symposium "Etiology of Myocardial Infarction," Detroit. Thomas N. James, Henry Ford Hospital, Detroit 2, Michigan.

November 27-30: American Medical Association, Clinical Meeting, Denver. F.J.L. Blasingame, 535 N. Dearborn, Chicago 10, Illinois.

December 1-2: Symposium on Cinefluorography (3rd) Rochester, New York. Stanley M. Rogoff, University of Rochester Medical Center, Rochester 20, New York.

Abroad

June 23-25: Italian Society of Cardiology, 22nd Congress, Sanremo. Secretary, Azienda Autonoma Soggiorno, Sanremo, Italy.

August 22-25: International Pharmacological Meeting (First) Stockholm. A. Wretlind, Karolinska Institutet, Stockholm 60, Sweden.

August 28-September 2: European Society of Haematology, Vienna. H. Fleischhacker, Wien IX Frankgasse 8, Billrothhaus, Austria.

September 3-7: International Congress on Rheumatology, Rome. Prof. C. B. Ballabio, Clinica Medica Generale, Via F. Sforza 35, Milano, Italy.

September 3-10: Inter-American Congress of Radiology, Sao Paulo, W. Bomfim-Pontes, Rua Cesario Motta, No. 112, Sao Paulo, Brazil.

September 4-9: International Congress of Angiology, Prague. Prof. Z. Reinis, IVth Medical Clinic, Praha 2/499, Czechoslovakia.

September 6-12: International Congress of Human Geneties, Rome. Luigi Gedda, 5 Piazza Galeno, Rome, Italy.

September 7-9: International Cardiovascular Society Congress (5th), Dublin. H. Haimovici, 715 Park Ave., New York 21, New York.

September 10-15: International Neurological Congress, Rome. G. Alema, Vialo Universita 30, Rome, Italy.

1962

October 7-13: Fourth World Congress of Cardiology, Mexico City. I. Costero, Secretary General, Ave. Cuauhtemoc 300, Mexico, D. F.

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CIRCULATION

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